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CONTENTS

	PAGE
Electrocardiographic Findings in Anemia . . . By P. Szekely	1
U, The Sixth Wave of the Electrocardiogram . By Cornelio Papp	9
The Psychological Treatment of Cases with Cardiac Pain By Geoffrey Bourne and E. Wittkower	25
Analysis of Fifty Normal Electrocardiograms including Lead IV By Jenner Hoskin and P. Jonescu	33
Electrical Axis Deviation of Fifty Normal Electrocardiograms By Jenner Hoskin and P. Jonescu	47
The Relative Value of Certain Digitalis Preparations in Heart Failure with Auricular Fibrillation . . . By William Evans	51

ELECTROCARDIOGRAPHIC FINDINGS IN ANÆMIA

BY

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It has been known for a long time that anæmia is occasionally associated with cardiovascular disturbances, especially with functional cardiac signs and symptoms and with angina pectoris, but there is still a wide diversity of opinion as to the frequency with which this occurs. Detailed electrocardiographic studies have been made less frequently, and so in the present publication such changes are described in cases of pernicious, acute posthæmorrhagic, and chronic hypochromic anæmias, and the conditions in which they occur are discussed.

Review of Published Cases

Herrick and Nuzum (1918) first pointed out that anæmia may be accompanied by angina pectoris, and reported some cases of pernicious anæmia in which anginal pain occurred after effort. Similar cases have been described later by many authors. Coombs (1926) observed typical attacks of angina pectoris in 8 of 36 cases of pernicious anæmia. Lewis (1934) considered angina pectoris as a frequent complication of anæmia, but Willius and Giffin (1927) found only 43 cases with angina pectoris among 1560 cases of pernicious anæmia. Hochrein (1932) and Scherf (1932) stated that anæmia alone causes neither anginal pain nor myocardial damage, and that the occasional disturbances of the coronary circulation in anæmia are always due to organic disease of the coronary arteries. Jagič and Flaum (1935) supposed that there is always a pre-existent latent myocardial damage which becomes manifest in anæmia.

Electrocardiographic changes in anæmia were mentioned by Ussoff (1911) and later by Coombs (1926). But systematic electrocardiographic studies in anæmia have been made only by later authors. Šerf (1929) found in some cases of pernicious anæmia a flat or isoelectric T wave. Turner (1932) observed low voltage in a great number of cases of pernicious anæmia. Elliot (1934) found in one case of anæmia a slight depression of the S-T segment in leads I and II associated with angina pectoris. He concluded that these findings may be the expression of a functional change resulting from anoxæmia of the myocardium. Bloch (1938) found among 88 cases of anæmia electrocardiographic changes in 47 ; most frequently flattening of the T wave (in

87 per cent. of the positive cases), less frequently depression of the S-T segment and low voltage. De Matteis (1936) studied 32 cases of anæmia ; in 18 of them there were abnormalities, especially changes in the T wave, and it may be of interest that 5 of these 18 were from eighteen to thirty years old, and 10 were younger than fifty years old. Marchal, Soulié, and Roy (1935) reported a case of severe posthæmorrhagic anæmia with low voltage ; immediately after blood transfusion a marked elevation of all waves could be observed. Parade (1933), Bloch (1934), Büchner (1939), Büchner, Weber, and Haager (1935), Aschenbrenner (1934), Herles (1934), Székely (1938), Marchal, Soulié, and Roy (1935), and Dassen and Parodi (1936) have all reported cases in which the electrocardiographic changes disappeared after improvement of the anæmia under treatment.

On the other hand, there are many authors who did not observe any, or only very insignificant, electrocardiographic abnormalities in anæmia, even in those cases in which angina pectoris or intermittent claudication occurred (Reid, 1923 ; Willius and Giffin, 1927 ; Shirley Smith, 1933 ; Pickering and Wayne, 1934 ; Hochrein and Mathes, 1934 ; Misske and Otto, 1937).

Present Observations

Electrocardiographic studies were made in 76 selected cases of anæmia in which clinical examination did not reveal any signs of disturbances of the cardiovascular system, or of any extracardiac affection that may also produce electrocardiographic changes. Cases associated with hyperthyroidism and pulmonary diseases were excluded. The material consisted of 32 cases with pernicious anæmia and 44 with secondary anæmia of the hypochromic type. The erythrocyte count ranged from 850,000 per c.mm. before treatment had begun, to 3,500,000 c.mm., and the value of hæmoglobin from 22 to 75 per cent. We were aware that the majority of the cases of pernicious anæmia were aged patients in whom slight sclerotic involvement of the coronary arteries giving rise to electrocardiographic changes could not be with certainty excluded, in spite of normal clinical findings. But on the other hand, the average age of the patients with electrocardiographic changes was 47·8 years and of those without such changes 44·7 years, which seems to justify the statement that the abnormalities could not be exclusively ascribed to the age and to latent coronary sclerosis. For considering the influence of anæmia on the coronary circulation those cases are of great importance, in which the clinical and electrocardiographic signs suggestive of disturbances of the coronary circulation were only transient and entirely disappeared when the anæmia improved, and those in which the anatomically normal state of the coronary arteries could be verified by post-mortem finding. But owing to the low mortality in anæmia such cases with anatomical verification are very sporadic.

Normal sinus rhythm was present in all cases except in two with auricular and ventricular extrasystoles respectively. The P-R interval was within the usual limits. Lengthening of the intraventricular conduction time was never observed. Left axis deviation was encountered in 10, right axis deviation in

4 cases. In general the following abnormalities were noted : (1) changes of the T wave ; (2) depression of the S-T segment ; and (3) low voltage.

In the series of 32 cases of pernicious anæmia there were electrocardiographic abnormalities in 11 (34 per cent.). The alteration of the T wave was the most frequent abnormality observed. It was seen in 8 cases ; in 2 there was a flat T in leads I and II, in 3 a flat T in leads I, II, and IV, in 2 there was an isoelectric T wave in the three standard leads, and in 1 there was an inverted T in lead I and a flat T in lead II. Depression of the S-T segment was observed in 5 cases and low voltage in 2 cases. Præcordial pain was noted in this group in four cases, but in only one did it have the typical clinical picture, characteristic of angina pectoris. This case had an inverted T wave, especially well marked during the attacks. After improvement of the anæmia, both the anginal pain and the electrocardiographic abnormality entirely disappeared. This case has been followed in our clinic and reported by Prusík and Herles (1934). In the three other cases with præcordial pain the electrocardiogram was normal at rest ; in two of them it was normal even after bodily exercise; in one case there was a slight depression of the S-T segment in leads I and II immediately after exercise.

Among 44 cases of hypochromic anæmia there were electrocardiographic changes in 12 (31 per cent.). In this group also the most frequent abnormality was an alteration of the T wave. It was abnormal in 12 cases ; in 5 it was flat in leads I, II, and III (these changes were associated with low voltage of the initial ventricular complex) ; in 4 it was flat in leads I and II, in 2 in leads I, II, and IV, and in 1 case it was inverted in leads II and III. Depression of the S-T segment in leads I and II was observed in 2, and low voltage in 5 cases. One case with occasional præcordial pain, which had a normal electrocardiogram at rest, but a slight depression of the S-T segment in leads I and II immediately after exercise, is not included. Low voltage was found exclusively in chronic and severe anæmia. From the five with low voltage in this group, two had myelogenous leucæmia which lasted twelve and sixteen months respectively, two had lymphatic leucæmia which lasted eight and ten months respectively. All these four patients were treated by X-rays before our study. The fifth case with low voltage presented clinically an " idiopathic " septicæmia in which the blood culture was repeatedly negative. Anginal pain occurred only in one case in which the electrocardiogram was normal at rest, but slightly pathological after exercise. The other cases of this group were free of anginal pain.

The frequency of the different electrocardiographic changes found in our cases of anæmia is summarized in Table I.

Except in a few cases, repeated electrocardiograms were taken and correlated with the hæmatological condition. No direct relation was found between the degree of anæmia and the electrocardiographic changes. There were cases in our series in which the red blood cell count and also the hæmoglobin were very low (a million or less and 22 per cent. respectively) and yet the electrocardiogram was normal. On the other hand, there were cases of only slight anæmia with marked changes. Neither the red blood cell count nor the hæmoglobin value were found to be in direct relation to the electrocardiographic changes.

TABLE I

CASES OF ANÆMIA WITH ELECTROCARDIOGRAPHIC CHANGES

Number of Cases and Type of Anæmia	Changes of the T Wave			Depression of the S-T Segment	Low Voltage
	Flat	Iso-electric	Nega-tive		
Pernicious Anæmia ; 11 cases ..	5	2	1	5	2
Hypochromic Anæmia ; 12 cases ..	11	0	1	2	5
Total ; 23 cases	16	2	2	7	7
Percentage	87·3			30·4	30·4

However, in some instances the latter entirely disappeared after improvement of the anæmia under specific treatment. In three cases a pathological T wave became normal, and in three a depressed S-T segment became isoelectric.

One case is reported, of interest both from clinical and electrocardiographic point of view, which may help to explain why severe chronic anæmia does not always produce disturbances of the coronary circulation, and on the contrary why anæmia of moderate degree sometimes results in coronary insufficiency. A man, 34 years old, who had never been ill, complained of slight abdominal pain, symptoms having started suddenly three days before with a profuse hæmatemesis. The heart was normal in size, shape, sounds, rhythm, and rate ; and the blood pressure, 140/90 mm. The lungs were normal. There was no rise of temperature and the sedimentation rate of the erythrocytes was 10 mm. in the first hour and 25 mm. in the second hour. The urine contained no albumin and no sugar. The erythrocyte count was 2,910,000 per c.mm., the hæmoglobin 61 per cent. The leucocyte count was 8,800 per c.mm., of which 65 per cent. were mature polymorphonuclear cells, 5 per cent. stab forms, 23 per cent. lymphocytes, and 7 per cent. monocytes. The first electrocardiogram revealed sinus rhythm, a very slight depression of the S-T segment, a flat T_1, and an inverted T_2 and T_3 (Fig. 1A). Next day the inversion of T_2 and T_3 disappeared, only a flat T wave persisting (Fig. 1B). An electrocardiogram five days later was entirely normal (Fig. 1C). The erythrocyte count the same day was 3,080,000 and later 4,100,000 per c.mm. Electrocardiograms were repeatedly taken and all were normal, including one taken after exercise.

DISCUSSION AND COMMENT

Experimental studies in animals have proved that anæmia may produce ischæmic disturbances of the myocardium, even when the coronary arteries are anatomically intact. Büchner (1932 and 1939) found in rabbits, after an acute massive venesection and artificially provoked exercise, marked changes (depression

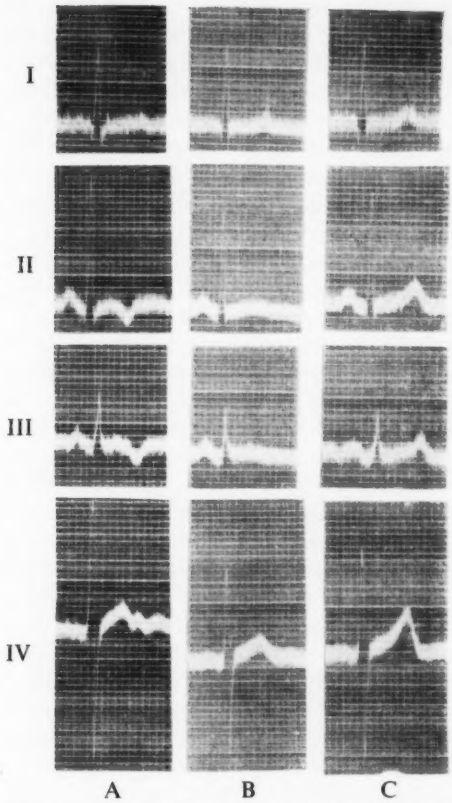

FIG. 1.—(A) Inversion of T_2 and T_3 with hæmoglobin of 60 per cent. (B) T_2 and T_3 flat, one day later, and (C) T_2 and T_3 upright, after six days.

of the S-T segment) which gradually disappeared ; and when these animals were killed after a few days he could demonstrate small areas of recent necrosis in their heart muscle. When they were killed during the first hours after the venesection and exercise, no anatomical changes of the myocardium were found. This author and others (Greene and Gilbert, 1921 ; Rothschild and Kissin, 1932–3 ; and Levy, Barach, and Bruenn, 1938), who experimentally induced anoxæmia and studied the electrocardiogram, found that the specific changes reached their culminating point during the acute oxygen deficiency and disappeared when normal oxygen supply was restored. Ischæmic necrosis of the heart muscle in animals was observed by Büchner only several hours after the condition of supposed acute coronary insufficiency. He concluded that the electrocardiographic changes in these cases are not due to the heart muscle necrosis, but purely to metabolic disturbances of the myocardium resulting from oxygen deficiency, which in anæmia may be caused by diminution of the oxygen-carrying power of the blood.

Laubry and Tzanck (1930) and Marchal *et al.* (1938) pointed out that the pathogenesis of cardiac disturbances seems to be different in acute posthæmorrhagic anæmia and in chronic anæmia. In the first group the anoxæmia of the myocardium is not a decisive factor, but only developes secondarily. The chief and direct cause of the cardiac disturbances may be the insufficiency of the return circulation (insuffisance de la circulation de retour). They could observe that the restoration of the volume of the blood by transfusion or by administration of physiological salt solution was followed by improvement of the clinical signs of cardiac damage and by disappearance of the electrocardiographic abnormalities. On the other hand, in cases of chronic anæmia they attributed a great importance to the anoxæmia of the heart muscle and considered it as the causal factor of cardiac disturbances.

Radnai (1935) made electrocardiographic studies in rabbits after venesection and found approximatively the same progressive changes which were later found by Marchal, Soulié, and Baugé (1938) : accentuation of the T wave, depression of the S-T segment, inversion of the T wave, appearance of a Q wave in lead III, and diminution and enlargement of QRS. Radnai emphasized the identity of these progressive electrocardiographic abnormalities with those found in angina pectoris and considered them anoxæmic in origin.

Experimental findings can only be applied with reserve in the clinical field. Nevertheless there are important clinical facts suggestive of a correlation between anæmia and cardiac disturbances resulting from anoxæmia of the heart muscle ; especially the occasional disappearance of both clinical and electrocardiographic abnormalities after improvement of the anæmia. However, in our cases there was no close parallelism between the degree of anæmia and that of cardiac disturbances. It seems probable that both in acute and chronic anæmia, angina pectoris or electrocardiographic changes are not due merely to the anæmia causing anoxæmia of the heart muscle, but also to another factor. And only the combination of these two factors results in cardiac disturbances. In cases of acute posthæmorrhagic anæmia this additional factor seems to be of reflex vasomotor character. In such instances the coronary volume flow may not be adapted to the acutely altered circulation and acute coronary insufficiency may result with clinical or electrocardiographic manifestations. We believe that our case of acute posthæmorrhagic anæmia, in which the coronary signs in the electrocardiogram entirely disappeared while only a mild improvement of the anæmia was observed, could be explained in this way.

In chronic anæmia the primary myocardial anoxæmia as the direct result of the diminution of the oxygen-carrying power of the blood may play a more decisive role. The experimental results of Marchal *et al* (1938) and of Radnai (1935) may be also in favour of this conception. The small fractional venesections with constant replacement of the volume of the blood by adequate doses of physiological solution may produce, indeed, an important diminution in the hæmoglobin with conservation of the normal blood volume, a condition similar to that in chronic anæmia. And in this experimentally induced anæmia in animals the same electrocardiographic changes were found, especially

flattening of the T wave and depression of the S-T segment, and less frequently low voltage, as in certain cases of chronic anæmia in men. But besides the anoxæmic damage of the heart muscle in chronic anæmia, toxic factors must be also taken into consideration as they may affect the myocardium directly. This might be the fact in our chronic cases with low voltage cases in which the electrocardiographic abnormalities were irreversible in spite of temporary improvement of the anæmia.

Summary

Electrocardiographic studies were made in 76 selected cases of anæmia in which there was no clinical evidence of cardiovascular disease. Electrocardiographic abnormalities were found in 23 cases. Most frequently flattening of the T wave occurred ; less frequently depression of the S-T segment and low voltage.

A case is reported of hypochromic anæmia in which inversion of the T wave in leads II and III occurred after a profuse hæmatemesis. These electrocardiographic changes entirely disappeared at an early stage when only a small improvement of the anæmia had been observed.

The pathogenesis of electrocardiographic changes and of cardiac disturbances in general, in acute posthæmorrhagic and in chronic forms of anæmia, is discussed.

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U, THE SIXTH WAVE OF THE ELECTROCARDIOGRAM

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Einthoven (1906) was the first to mention the sixth or U wave of the electrocardiogram. In 1912 he found it in half the records he examined for this purpose. Lewis and Gilder (1912) first gave statistics of the U wave in healthy people, finding it in 90 per cent., most often in lead II, and of an average height of 0·16 mm. They saw it as a sharp peak immediately after T or as a shallow bending of the whole T-P period. Hering (1913) thought it was aortic and not cardiac in origin.

There are references in various textbooks. Hoffman (1914) described it as " produced by the passive movements of the heart . . . starting after the closure of the semilunar valves . . . belonging to the diastole." Kahn (1914) also thought it important in proving that the end of the electrical activity of the heart is not limited by the T wave. It is mentioned as frequently present (Wiggers, 1923) ; as of unknown meaning (Lewis, 1925) ; as of uncertain origin (Reid, 1928) ; and as of doubtful relationship to ventricular systole (Wenckebach and Winterberg, 1927). In the second edition of his book Pardee (1924) says : " A broad low wave, called U, is sometimes observed following T. It is probably not due to the heart at all, but is caused by the great vessels." There is no reference to it in his third edition (1933) or in the books of Weber (1926) or of Boden (1932).

Hoogewerf (1929), finding it in athletes, thought it might indicate a strong heart ; and Csinady (1930) had a similar impression. Maekawa (1931) studied the electrical events on the muscle strip of the frog's heart and registered the U wave. In human records he separated two types (already mentioned by Lewis and Gilder), of which the short and peak type was held to represent the physiological and the shallow and long type the pathological form. He saw a certain relation between the height of T and of U. Trendelenburg (1934) in various chest leads from normal persons found U always present in one or more leads. Though admittedly a normal wave, " it can become more apparent in cardiac hypertrophy." Gross (1934) agreed that it is a normal event and denied the interdependence of T and U. Hinden (1935) was one of the first to analyse a series of records showing large U waves. In his paper, with figures from the Heart Hospital and the London Hospital, he allowed no distinction in the

significance of the two forms mentioned by Maekawa, for both were found equally in healthy and in diseased subjects. Herles (1934) found large U waves in some records taken from dying human hearts, though his two figures are scarcely conclusive. Holzmann and Wuhrmann (1936) noted increased size of the U wave (as well as of P and T waves) after exertion. In several cases of Blumberger (1937) it was absent before exertion but appeared after it. Schulz (1938) suggested that a failure of U to appear after exertion might indicate a pathological "deactivation" (inactivationsprozess) in the heart. Székely (1938) found it largest in a chest lead ; there was no direct relation between hypertension and the U wave, but in coronary sclerosis it was less common than in other heart diseases or in healthy people.

Since this investigation was completed, a new and important article on the U wave has appeared, that of Nahum and Hoff (1939). Investigating the supernormal period of recovery in the mammalian heart, they found that the U wave coincided with it. While in tachycardia the period fell at the end of T, in bradycardia it appeared closely after T and became visible. In 75 per cent. of 151 normal human records and in 40 per cent. of 90 pathological records, a U wave of at least 0·25 mm. was found, using lead IV R. Its maximal height was 1·5 mm. and the average duration 0·20 sec. In pathological conditions it can be fused with T or can be inverted. The inverted U may be the only electrocardiographic sign of a damaged heart ; it was seen in coronary, rheumatic, hypertensive, and pulmonary heart disease, and was thought to be due to metabolic changes in the heart muscle, reflected in an altered shape of the after-potential. The frequent coincidence of extrasystoles with the U wave was considered a further proof that it is the electrical expression of the period of supernormal excitability.

Method of Investigation

From a large number of electrocardiograms those were selected in which U could be identified in the limb leads. In about 70 per cent. of normal cardiograms a deflection could be found in one or more leads on the diastolic line, but often so small that neither its dimension nor its duration could be measured. For this reason 0·5 mm. was chosen as the limit in height for this study. Using this rather strict criterion, the electrocardiograms showing U waves were reduced to about 5 per cent. of 2000 suitable consecutive records, excluding those with auricular fibrillation, flutter, and tachycardia above 110 a minute, in which conditions it proved impossible to identify the U wave.

The patients providing these selected records were studied with regard to the rate of the pulse, blood pressure, clinical diagnosis, and radiological appearances. The electrocardiogram was examined as to the systolic period and the distribution of the U wave in the different limb leads in health and disease. Investigations were also made on the action of digitalis and quinidine on the U wave.

The physiological U wave changes were watched in healthy men under various conditions. The limb leads proved unsuitable for studying the slight

changes that might appear under respiratory or effort tests, carotid compression, atropin, or amyl nitrite. Chest leads, especially the IV R standard lead, were used for this purpose. After trying the exploring (proximal) electrode on various sites on the chest wall—left pectoral (Wood and Selzer, 1939), base, and on or external to or internal to the apex—and the indifferent (distal) electrode on the back or on the left leg, it was found that the largest U wave deflections were obtained by lead IV R.

The U Wave in Health

The normal U wave is found at any age from 16 to 75 years, and sex seems to make no difference. At what age the wave appears is undecided. Papers on the electrocardiograms of normal children (Krumbhaar and Jenks, 1917 ; Seham, 1921 ; Lincoln and Nicolson, 1928 ; Bruce, 1931) do not mention it nor contain records showing it.

The height of the normal U wave in limb leads is from 0·10 to 1 mm., and its duration is from 0·16 to 0·24 sec. The shape of the wave—often only a slight hump of the diastolic line—and its variation in size and form in the same record make an exact description difficult. The normal U wave in lead IV R is

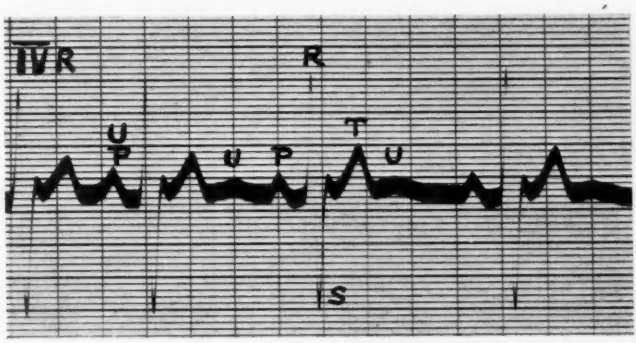

Fig. 1.—Electrocardiogram showing fusion of U and P in tachycardia ; with slowing of the heart rate they become dissociated.

upright, 0·5 to 2 mm. in height, with a duration of 0·18 to 0·24 sec., and begins before or closely after the end of T. Its visibility is notably influenced by the heart rate. In tachycardia (over 105–110), when T and the following P are close together, U becomes hidden in P. Indeed, the higher P in tachycardia may be reckoned as partly due to the fusion of P and U (Fig. 1). The first P of this record is 3 mm. high, the others are only 2 mm.

In bradycardia (under 60), the R-T period increases in duration. While with a rate of 80–90 the duration of the whole ventricular complex (from start of Q to the end of T) has an average value of 0·35 sec., with a rate of 52 the R-T period extends to 0·46 sec. (Pardee, 1933). In one of our healthy students, with a bradycardia of 54, the duration of the ventricular complex (Q-T) is generally 0·44 sec. The U wave appears on the record as a hump on the descending

branch of T (Fig. 2, A and C). This deformity of T is recognized as U when the duration of the systolic period (Q-T) decreases, as happens in the slight tachycardia following effort (Fig. 2 B). The maximal duration of the ventricular complex at which U can appear as an independent wave rising from the isoelectric line seems to be 0·40 sec. With a duration of 0·40 sec., U can be

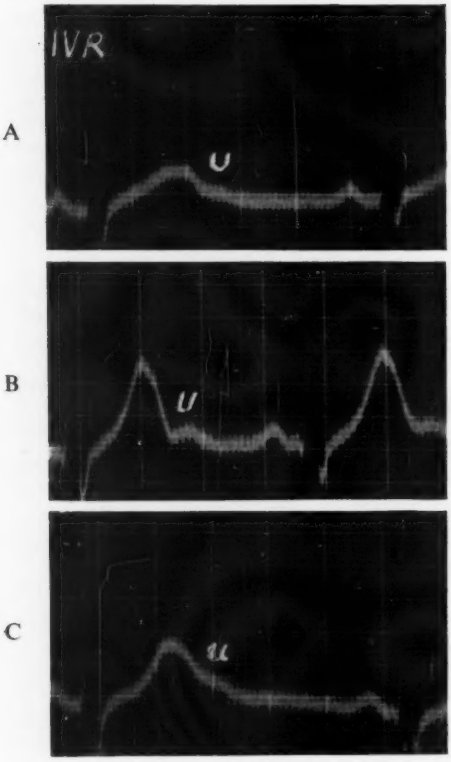

FIG. 2.—(A) Fusion of U and T in bradycardia, 54 a minute ; (B) separation of U from T in tachycardia from exertion, 76 a minute ; and (C) return to fusion of U with T three minutes later.

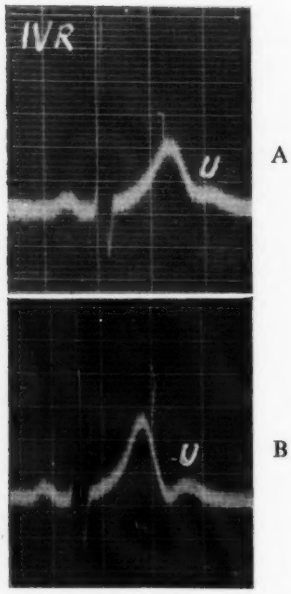

FIG. 3.—Separation of U and T by holding the breath (B), without change in rate.

partially hidden in T yet appear as an independent and larger wave at the end of a forced apnœa (held breath) (Fig. 3 B).

The fusion of U with P in cases of tachycardia or with T when the ventricular complex becomes prolonged prompts the question whether exact time relations between R and U can be established. This can only be answered by studying records in which exact measurements are possible. It is only when U has a sudden onset or is peak-shaped or finishes abruptly on the isoelectric line that R and U time relations can be at all exactly established. Two of the experimental records proved suitable. In one, in which the R–T interval varied

between 0·36 and 0·43 sec. owing to the change in rate with respiration or exercise, the interval R to U peak showed the remarkable stability of 0·42 to 0·44 sec. In the other, the R–U (end) interval of 0·56 sec. remained nearly unchanged when the rate from 52 rose to 72, although the R–T (end) interval decreased from 0·46 to 0·36 sec. Thus the stability of the R–U allows us to consider U as independent of T, to establish certain relations between QRS and U, and to deny any regular time relation between T and U. Respiratory changes of U are seen in sinus arrhythmia ; during inspiration it increases in height and becomes shorter in time, and during expiration it becomes flatter and its duration is prolonged. In such variations one can find in the same record the two types of wave described by Lewis and Gilder (1912) (see Fig. 4). Thus the statement

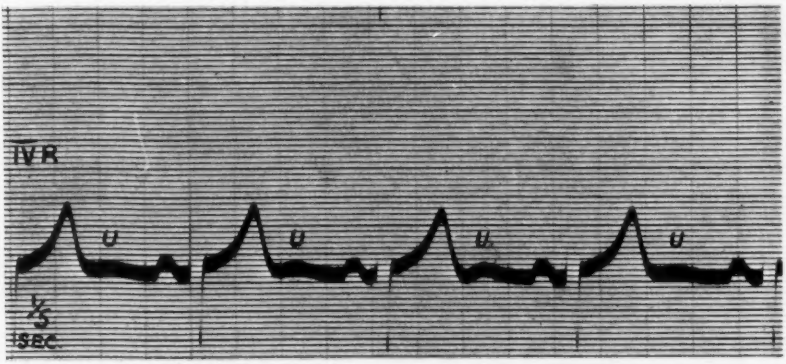

FIG. 4.—Respiratory variations of U. It is sharper and shorter during inspiration.

made by Maekawa (1931) and denied by Hinden (1935), that the short and peaked U is the normal and the large and flat is the pathological U wave, is unfounded.

FURTHER OBSERVATIONS ON HEALTHY MEN

The standard lead IV R was used and the experimental results are given in Table I. Nearly constant experimental results have been obtained on exercise

TABLE I

CHANGES IN THE SIZE OF THE U WAVE UNDER VARIOUS CONDITIONS IN FIVE HEALTHY YOUNG MEN

On Exercise	After 3 minutes	Normal Respiration	Deep Breath	Breath Held	Carotid Compression
+	+ +	R	O	O	–
+	+	O	–	+ +	–
+	+	O	O	+	O
+ +	+	O	–	O	– –
+ +	+	R	O	+	+

+ + = increase by more than 0·5 mm.
+ = slight increase.
– = decreased.
– – = disappeared.
O = no change.
R = respiratory changes.

(20 knee-bendings), both immediately after and three minutes later. The increase in the size of U on effort does not seem to be due to tachycardia. It remains increased after the tachycardia has ceased and can also be found where there is little or no acceleration after effort. The two cases which showed diminution of U on deep breathing showed the same after carotid compression ; in one of them U disappeared, in the other it diminished.

Both methods, especially the latter, produce vagal excitation. The vagal release by atropin (1/50 grain, i.e. 1·3 mg., subcutaneously) had no effect on the U wave in the four observations made. Amyl nitrite was administered in all five cases, but the resultant tachycardia nullified the observations on the U wave. Forced apnœa produced in three of five cases an enlargement of the U wave, most noticeable when the subject could no longer hold his breath.

Increase in height of U is almost always accompanied by increase in the

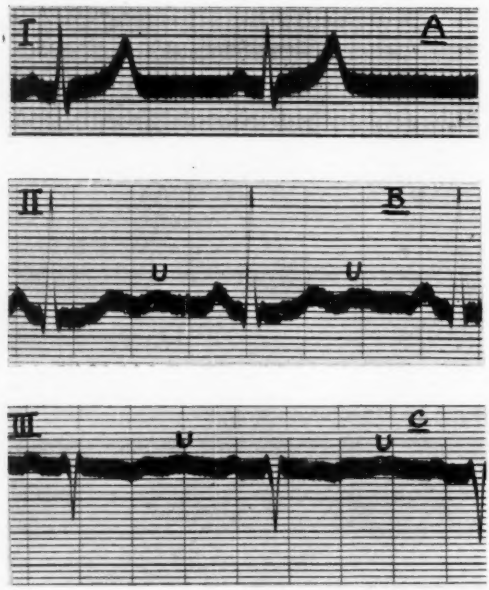

FIG. 5.—Relative independence of size of U and T. Records from three healthy men ; (A) U absent with large T ; (B) U almost as large as T ; (C) U upright after diphasic T.

height of T. The T wave not only enlarges, but changes its shape and becomes rather pointed, especially after effort. Yet in normal conditions big U waves are often observed following small or even inverted T waves (Fig. 5).

THE U WAVE IN DISEASE

A. The Upright U Wave

One hundred consecutive records of patients with heart disease were examined, records in which the U wave was 0·5 mm. high or more in at least one of the three standard limb leads.

1. *Heart Rate.*—This has little importance except that U is scarcely to be identified at rates above 110, as shown by the following figures.

Heart rate per minute	Number of cases in which the U wave was present
40–60	13
60–80	38
80–100	43
above 100	6

2. *Systolic Blood Pressure.*—The frequent incidence (47 per cent.) of hypertension among patients showing a large U is evident from this table.

Systolic Blood Pressure in mm. Hg.	Number of cases in which the U wave was present
90–110	2
110–130	23
130–160	28
160–200	32
over 200	15

3. *Clinical Diagnosis.*—Hypertension in its three groupings is seen to account for no less than 37 per cent., compared with 17 per cent. without heart disease.

Clinical Diagnosis	Number of cases with U wave
No cardiac disease	17
Hypertension without much enlargement	13
Hypertension with cardiac enlargement	19
Hypertension and cardiac failure	5
After Digitalis treatment	11
Extrasystoles	8
Coronary thrombosis and Angina pectoris	11
Thyrotoxicosis	6
Valvular Disease	10

Incidentally, Spang and Korth (1939) found that 20 out of 200 thyrotoxic cases had pronounced U waves in limb leads. Some relationship between the left ventricle and the U wave is suggested by its frequency in conditions affecting the left ventricle, and also by the fact that lead IV R (pertaining especially to the left ventricle) is favourable for its demonstration. It was easy to find among young and athletic students many with large U waves. This bears on the statements of Csinady (1930) and Hoogewerf (1929). Bramwell and Ellis's (1931) paper contains records of two long-distance runners with prominent U waves. Congenital heart disease seldom shows records with large U waves, even where all the ventricular deflections are greatly enlarged in the right axis deviation.

Heart Failure.—Besides the five cases of hypertensive failure quoted, fifty other cases of failure with normal rhythm were examined and in three only was U present before digitalis therapy. In four others in this extra series it appeared only after digitalis. In general, U tends to be less frequent and smaller in heart failure (certainly left) than in its absence.

Digitalis.—In 11 cases U was seen only after digitalis treatment, but in 6 of these there had been tachycardia, fibrillation, or flutter, which would have

prevented its recognition even if present. The remaining 5 show that it may be accentuated or even produced by digitalis (Fig. 6). No effect on the U wave was noticed even after prolonged administration of quinidine.

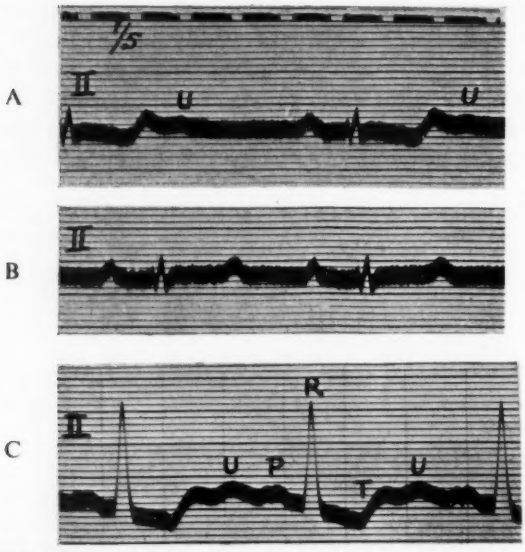

FIG. 6.—Digitalis effects. (A) The U wave is well seen after full doses of digitalis ; and (B) absent four weeks after it was stopped ; (C) Very large U waves following prolonged digitalis administration.

4. *X-ray Findings.*

X-ray Findings	Number of cases with U Wave
Normal heart	45
Slight if any enlargement	12
Slight enlargement of left ventricle	16
Moderate enlargement of left ventricle	17
Enlargement of right and left ventricle	6
Characteristic of mitral stenosis	4

5. *Electrocardiographic Findings.*—In half the hundred records showing a large U the electrocardiogram was normal. When abnormal, the change usually concerned the T waves. In 32 with flattened or inverted T, U was upright—a fact which stresses their independence in disease as already described in health.

Electrocardiogram	Number of cases with U Wave	
	Upright	Inverted
Normal	50	0
Left axis deviation	6	0
Right axis deviation	1	0
T_1, T_2 changes from Hypertension	14	4
T_1, T_2 changes from Coronary disease	12	2
T_2, T_3 changes from Coronary disease	5	2
R–T depression (digitalis)	3	0
A–V dissociation	1	0

The systolic period R–T showed, using Pardee's table (Pardee, 1933), in 78 per cent. a normal value, in 14 per cent. slight prolongation, and in 8 per cent. distinct prolongation. Contrary to the opinion of Einthoven (1912) and Maekawa (1931), therefore, no relationship was found between the presence of U and the lengthening of systole.

6. *Distribution of Upright U in Leads I, II, and III.*—U appears most often in lead II, and it was present in this lead in 87 per cent. While U in lead II was found equally in normal and in pathological records, the isolated appearance of U in leads I or III was, with one exception, in pathological records.

	Cases	U_1	U_2	$U_{1,2}$	$U_{2,3}$
Normal electrocardiogram	55	1	44	8†	2
Left axis deviation	6	—	4	1†	1
Right axis deviation	2	—	—	2	—
T_1, T_2 changes in hypertension	14	1	10*	2	1
T_1, T_2 changes in coronary disease	13	4	9*	—	—
T_2, T_3 changes in coronary disease	5	2	3*	—	—
R–T depression (digitalis)	5	1	3*	1	—
	100	9	73	14	4

* Including in each case one with U_3 only.
† Including in each case one with U_1, U_2, and U_3.

B. The Inverted U Wave

In 8 per cent. of the series an inverted U wave was seen in the limb leads, and it could always be confirmed in lead IV R. The patients concerned had coronary thrombosis (5 cases, 3 with hypertension) or hypertension alone (3 cases). With one exception T changes were always present. Three cases of coronary thrombosis were of the T_1 type, and two cases of the T_3 type (Fig. 7).

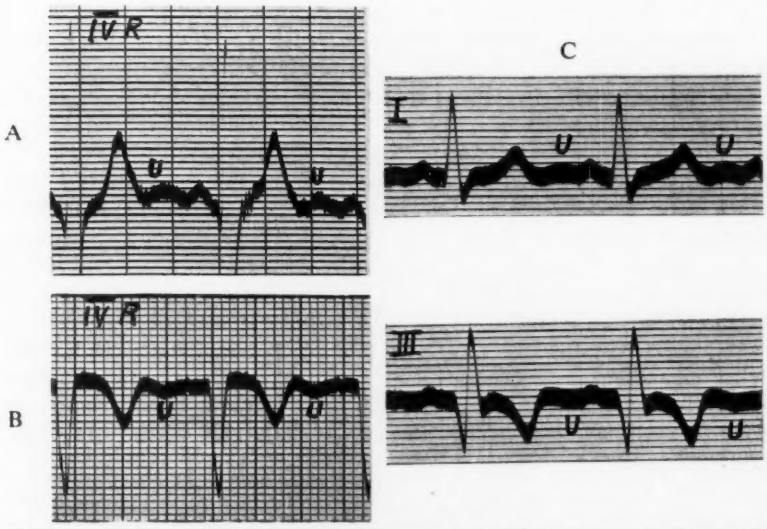

FIG. 7.—(A) Before, and (B) three weeks after coronary thrombosis, to show inversion of the U wave. T_1 was also inverted (anterior infarct). U is identified by measurement from R or from S; (C) three weeks after posterior coronary thrombosis in another case.

A transition stage from upright to inverted U is shown in Fig. 8, where U is diphasic in IV R.

FIG. 8.—Diphasic U in lead IV R with upright U in lead II.

Inversion of the U has never been seen by me nor has it ever been reported in a normal electrocardiogram, so must be considered pathological. This new sign, not previously described except by Nahum and Hoff (1939), may become of some clinical value. It may prove the only pathological sign (Fig. 9).

With Extrasystoles and Bundle Branch Block

If ventricular extrasystoles are accompanied by a U wave, this is often upright ; but where the S component is inverted, U may be inverted. U is seldom seen in pathological bundle branch block ; and among 60 such cases it was only seen in four limb lead records. This rarity can scarcely be due to the long duration of the ventricular complex, for this rarely exceeds 0·40 sec., a period which would permit its recognition. In the common type of bundle branch block the U wave is generally inverted in lead I and upright in lead III. following the direction of S (Fig. 10). Comparing records from two patients, the one without failure showed U only in left pectoral–R (Wood and Selzer, 1939), but the other with failure, using the same lead, did not. U was never seen in bundle branch block with failure.

In bundle branch block with a short P–R interval, the so-called Wolff, Parkinson, and White syndrome (1930), there may be a reversion of the short P–R wide QRS complexes to normal complexes. The U wave, when absent in the former, may be evident in the latter (Tung, 1936 ; Fig. 8 in Wolff, Parkinson, and White, 1930).

RECOGNITION OF THE U WAVE

This may be difficult in simple bradycardia or tachycardia owing to its fusion with T or P respectively (Fig. 1, 2, & 3). When in tachycardia the T–P

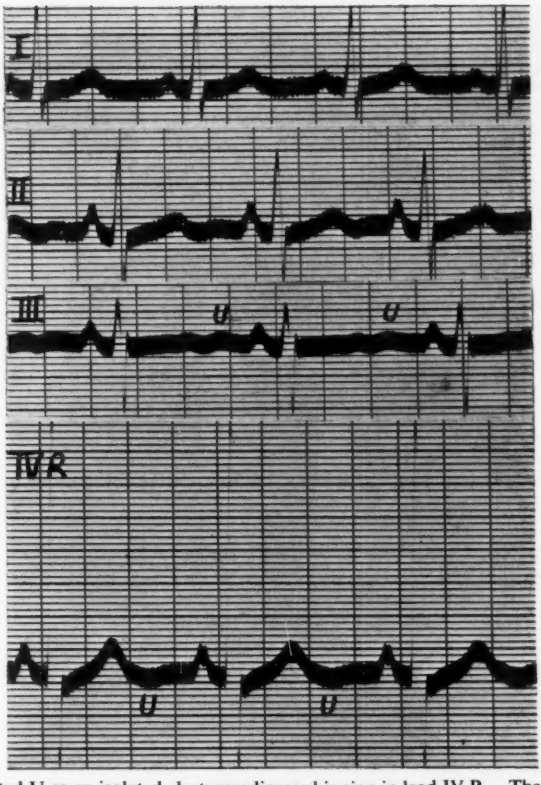

FIG. 9.—Inverted U as an isolated electrocardiographic sign in lead IV R. The R–U distance in leads III and IV R is the same ; from a man with hypertension and angina of effort.

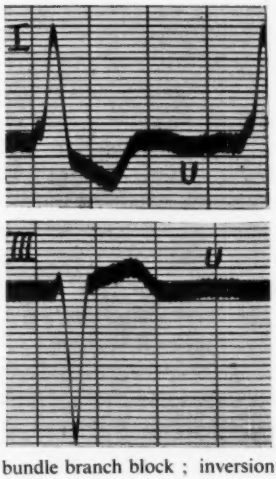

FIG. 10.—Left bundle branch block ; inversion of U in lead I.

distance has the same length as a large U wave, the curve may resemble that of auricular flutter. A premature auricular beat with blocked ventricular complex may look like a U wave, but there is a compensatory pause to be explained. The greatest difficulties, however, arise in the rare cases of bifid T wave. Such a wave may be followed by U, so that there are three upright deflections between

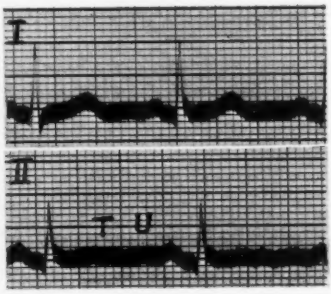

FIG. 11.—Presence of bifid T along with U. The R–T distance, measured in lead I, covers T but not U in lead II.

R and P (Fig. 11). In this record, the R–T (end) distance in lead I, measured on lead II, shows that the second deflection after R must be included as part of T.

INTERPRETATION OF THE U WAVE

The several hypotheses advanced to explain the U wave may first be divided into the extracardiac and the cardiac.

1. *Extracardiac hypotheses.*—Hering (1913) viewed the U wave as the electrical expression of the aortic contraction. Lewis (1915) disagreed, finding its occurrence so long after the carotid pulse incompatible with an aortic source. Trendelenburg (1934), knowing that an electric current may be generated at the end of systole by a rapid blood flow, thought that this might account for it. All subsequent evidence has been against this view, which also may be dismissed. Similarly there is no evidence that the swing of the heart during diastole could originate such an electrical disturbance as the U wave manifests.

2. *Cardiac hypotheses.*—The almost constant time relation with QRS, a certain but limited correspondence with the size and direction of T, and the influence on U of several factors that also affect the heart, all go to prove that the U wave is part of the electrical expression of cardiac activity or an immediate consequence of it. Its position on the borderline between systole and diastole raises the important question, to which of these does it belong ? According to Einthoven (1912) and Maekawa (1931), the main part of the heart muscle is already in a state of relaxation when U appears, but a few muscle fibres are still in contraction: it would then be the expression of a "dying away of the contraction," a systolic product though appearing early during diastole. On the other hand, Lewis and Gilder (1912), Trendelenburg (1934), and Lewis (1937) regard U as belonging to diastole. Its position in relation to the polygraphic (venous

pulse) tracing should enable us to place it correctly in regard to the cardiac cycle. With a normal heart rate, it begins coincidently with the peak of the " v " wave or somewhat later, i.e., after the opening of the A–V valves (Fig. 30, Lewis, 1925), and not with the ascending portion of " v " as presented in the diagram by Lewis (1925) (his Fig. 24). Not only by reference to his Fig. 30, but by measurement of our similar figure (Fig. 12) the coincidence of U with the peak

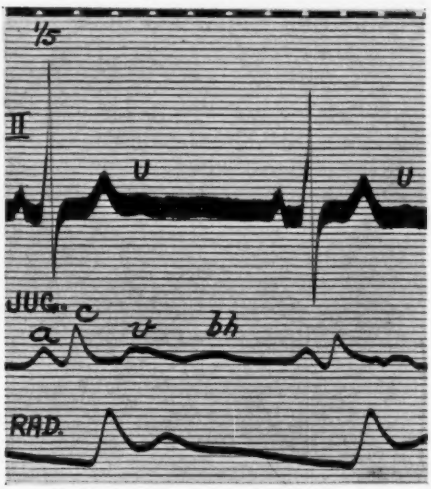

FIG. 12.—Combined electrocardiogram, jugular, and radial tracing. U coincides with the fall of " v " ; and occurs long before the " b h " wave.

or downstroke of " v " can be established. Its appearance in the early stage of diastole, and its evident time relation with " v " exclude any relation between U and the " b h " wave of the venous tracing which does not appear until late in diastole. It is found only in slowly acting hearts and is due to the floating up and transient closure of the tricuspid valves when the blood flows into the ventricle (Mackenzie, 1925). The first part of diastole has been termed by Luciani (1911) active diastole. Lewis (1925) refers to the second part of diastole, after the opening of the A–V valves, as diastasis. Even assuming a remnant of muscular activity in the first part of diastole, i.e., the post-sphygmic period that is the interval between the closure of the semilunar and the opening of the A–V valves, this could not be represented by the U wave ; for its appearance after the opening of the A–V valves (the peak of the venous " v " wave) rules out this explanation.

The simple fact of U often beginning before the end of T, so as to deform it (Figs. 2 and 3), suggests at once that it can begin before systole is over, accepting the end of T as the end of systolic contraction. In the U wave we seem to have an electrical component, independent of both systole and diastole, arising sometimes before and sometimes after the end of T. Simultaneous records of

the end of T with a phonocardiogram of the second heart sound might help to decide, were U waves present in such a combined record.

A certain similarity between the shape and direction of T and U and their similar response in experiment seem to suggest that they have a common origin, or at least that U is derived in some way from the T wave. Strongly against this explanation, however, is the common appearance of U in bradycardia on the descending portion of T, i.e., before systole is over. As the end of T marks the end of systolic contraction, U might be a sequel of that contraction. Nahum and Hoff (1939) in this sense speak of U as the expression of the phase of recovery, after the refractory period. If so, U on this hypothesis should always have a direct time relation to T or to the end of T. But the facts are to the contrary : U may as easily deform T as follow it, according to the simple factor of rate. The truth is that U is related in time to QRS and not to T. Once the Q-end T period is determined, a period which varies chiefly with rate, U may be recognized as : (a) a hump on the downstroke of T, at a rate below 60, i.e., when the Q-end T period exceeds 0·40 sec. ; (b) an isolated wave, upright or inverted, at a normal or moderately high rate (60 to 110), i.e., when the Q-end T period is from 0·40 to 0·34 sec. ; (c) partially or totally fused with the succeeding P at a rate above 110, i.e., when the Q-end T period is 0·34 sec. or less. The contrast lies between the relative fixity of the Q–U period, measuring 0·38–0·42 sec., and the variability of the Q–T period measuring between 0·34 and 0·46 sec. at different heart rates. The idea that U disappears with change of rate is incorrect. When it is not identified as a separate wave, it still may be present, fused with the succeeding P and elevating it correspondingly (Fig. 1).

Though existing hypotheses advanced to explain the U wave have been criticized and even rejected, I am unable to offer anything more satisfactory. Its closer time relation with the QRS complex than with T, and its beginning, sometimes before and sometimes after systole is completed, seem to exclude simple or direct relation to the muscular contraction of the heart. The U wave may represent an electrical event in the heart muscle, so far novel and unrecognized, which is not the expression of a kinetic activity and so not directly related to the heart rate.

Summary

Observations have been made on the incidence, appearance, and variations of the U wave of the human electrocardiogram in health and disease ; and its genesis is discussed.

1. *The U Wave in Health*

In about 70 per cent. of normal records U is present in one or more limb leads, and in about 5 per cent. it is at least 0·5 mm. in height. It is often larger in special chest leads, especially in IV R, in which it may be 0·25 to 2·0 mm. high and 0·18 to 0·24 sec. in duration.

In tachycardia, it is fused with the succeeding P. In bradycardia with its lengthened S–T period, it overlaps T, forming a hump on its descending portion.

It follows that U is related in time to QRS and not to T ; it tends to fuse with T when the Q–T period is longer than 0·40 sec. It varies with respiration, becoming sharper and shorter in inspiration, and flatter and longer in expiration. It enlarges after exertion and in forced apnœa. Vagal release by atropin influences it little if at all ; vagal stimulation (e.g., by carotid sinus compression) may exaggerate or may dissipate the wave.

2. *The U Wave in Disease*

Of 100 consecutive electrocardiograms in which U was higher than 0·5 mm. in limb leads, nearly half the patients had a blood pressure above 160 mm. and 40 per cent. showed enlargement of the left ventricle on radioscopy. A large U was less often seen with right ventricular enlargement. U tends to be absent in heart failure and may first be seen during recovery from it. Digitalis can enlarge a small U wave or produce one where none was seen before its administration. Though T and U may enlarge concurrently, there is otherwise little relation between them ; for instance, a large T may have a small U wave following it or vice versa.

An inverted U wave is the only pathological form yet recognized. It is to be found in coronary thrombosis, hypertension, angina pectoris, and aortic incompetence. Generally, it is found with an inverted T, though it can be the only pathological sign in an otherwise normal record.

After extrasystoles commonly, and in bundle branch block rarely, U may be seen, either upright or inverted. Where T is bifid, as occasionally it is, the identification of U may not be easy.

3. *Interpretation of the U Wave*

The idea of its extracardiac origin is untenable. The U wave is a product of cardiac contraction and has generally been held to occur after contraction has ceased, i.e., in diastole. At normal heart rates it appears early in diastole and coincides with the peak or the fall of the jugular " v " wave, i.e., while the A–V valves are open and therefore after systole is complete. It occurs well before the " b h " venous wave. Yet as the U wave in bradycardia begins before, and at a normal rate after the end of T, and in tachycardia is fused with the succeeding P, U may be envisaged not only as a more persistent wave than had been thought, but as an electrical event independent of both systole and diastole. The R–U period is relatively constant while the R–T period varies greatly with rate. This constant relation of U to R, the lack of relation of U to T, and the fact that a mere change in heart rate makes it seem at one time systolic and at another diastolic, render doubtful the interpretation of U either as a wave arising from muscle going out of contraction or as the electrical expression of a supernormal recovery phase.

Possibly U has a hitherto unknown quality in that it appears unattached to systole or to diastole, for it is independent of T and also curiously independent of the heart rate.

I feel greatly indebted to Dr. John Parkinson, Physician to the Cardiac Department, who suggested and promoted these investigations ; without his constant help they could not have been completed. My thanks are also due to Dr. Evan Bedford for permission to use material from the Middlesex Hospital, and to Dr. A. N. Drury of Cambridge for his advice.

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THE PSYCHOLOGICAL TREATMENT OF CASES WITH CARDIAC PAIN

BY

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In two papers published in 1937 (*The Lancet*, pp. 609 and 665) an attempt was made to assess the relative significance of emotional and organic factors in the production of cardiac pain. On examination of two groups of patients it was shown that four fifths of the first, i.e., patients with cardiac pain, as compared with one fifth of the second group, i.e., patients with cardiac deficiency but without pain, suffered from some psychological disorder before the appearance of cardiac symptoms. In a surprisingly high number of cases the cardiac pain seemed to emerge as a late component of a chronic anxiety state and its onset was often precipitated by some disturbing event in the patient's life. This sequence is familiar as far as functional pain is concerned, but it was also found in certain cases of angina of effort.

In continuance of these studies, a group of 12 patients with cardiac pain has been submitted during the past two years to psychological treatment, to find to what extent patients with functional cardiac pain might respond to this treatment, and if and how far cases of angina of effort, carefully selected because of a prominence of emotional problems in their histories, might be amenable to psychotherapy.

MATERIAL : SELECTION OF CASES

Seven patients complained of the type of pain previously described under the label angina innocens (*Brit. Med. J.* 1937, I, 695). Reference to that paper will make it clear that a cardiac condition, not an intercostal fibrositis, is referred to. For the purposes of the present paper the less controversial terms functional pain or functional cardiac pain are used; another synonym is left submammary pain.

Angina of effort has as its basic lesion coronary disease, but the degree of pain is proportional to the predisposition of the nervous system to make this manifest. Psychological treatment is thus rational in cases of angina of effort with psychological abnormalities.

Seven patients with functional pain, two men and five women, and five men with typical angina of effort form the basis of the present study. One

was a patient of Dr. Evan Bedford and the others were examined clinically and sent for treatment by Dr. Geoffrey Bourne. These cases have been selected with considerable care ; previous to treatment they had all been examined carefully and had been followed for lengths of time varying, in the functional cases, from one to four years and, in the patients with angina of effort, from two to thirteen years. The type of pain had been analysed according to the classification previously described (*Brit. Med. J.*, 1935 I, 1109). During the period before psychological treatment the diagnosis had thus been confirmed by many examinations. A number of patients were referred to Dr. Wittkower for an opinion as to their suitability for treatment and were rejected for reasons that will be explained later.

The clinical material fell into two groups, according to the type of pain present. In the group with functional pain were four cases with normal hearts, one with hyperpiesis, and two with mitral stenosis ; in the angina of effort group were two with no other severe cardiovascular abnormality, two with hyperpiesis, and one with aortic stenosis. The cases are summarized as follows.

Patients with Functional Pain

Case 1. A man, aged 54, had suffered from persistent severe pain in the left chest for three years. He had collapsed and fainted at the onset of the pain, and since then had complained of pain in the chest, radiating to the left arm. This was not quantitative to exertion or diminished by rest, but he was seen by a physician who told him that he had ' angina' and stopped him from working. On examination no cardiovascular abnormality was found, the electrocardiogram was normal, and the history of the pain was of the functional type. He was therefore reassured with regard to his heart and was referred for a psychological opinion and treatment. (See later.)

Case 2. A woman of 28, with early mitral stenosis, had for three years suffered from pain which had, at times, been very severe. It was on the left side of the chest and was worse when she was tired. She had suffered also from attacks of pain followed by faintness, although she did not lose consciousness. In such an attack she would feel as if the end had come. On examination there was an early mitral stenosis, confirmed by X-ray, but the electrocardiogram was normal.

Case 3. A woman of 22 had for the previous five years felt pain on exertion on the left side of the chest radiating to the neck and arm. It was increased after exertion but not during it, and was accentuated by worry and fatigue. There was no cardiovascular abnormality except slight accentuation of the first sound.

Case 4. A woman of 43 had suffered for some years from pain in the left side of the chest which was at first a severe sudden stab followed by a dull ache persisting for a few minutes. Subsequently it became more persistent but was never proportional to exertion. On examination there was marked enlargement of the heart, both to the right and to the left, mitral stenosis, and auricular fibrillation.

Case 5. A man of 39 had suffered from palpitation and exhaustion for three years. Exercise produced pain in the left side of the chest which was not quantitative to exertion. On examination he was found to have a blood pressure of 180/130. The electrocardiogram showed left-sided preponderance.

TABLE I

PATIENTS WITH FUNCTIONAL PAIN

Case number	Age and Sex	Diagnosis	Duration of Treatment		Result of Treatment		Follow-up	
			Physical (in years)	Psychological (in months)	Pain	Psychological symptoms	Duration (in months)	Results
1	54, M	Conversion hysteria	3	4	Lost	Lost	12	No complaints ; at work
2	28, F	Anxiety state, and mitral stenosis	10	3	Lost	Much improved	18	No complaints ; at work
3	29, F	Conversion hysteria	1	4	Lost	Much improved	12	No complaints
4	43, F	Anxiety state, and mitral stenosis	2	4	Lost	Much improved	18	Relapsed after 6 months with failure
5	39, M	Anxiety state, character disorder, and hyperpiesis	5	4	Lost	Much improved	6	Death after 8 months
6	28, F	Character disorder	4	4	No change	Unchanged	5	Improved later and at work
7	32, F	Conversion hysteria	2	9	Lost	Much improved	1	At work

Case 6. A woman of 28 had suffered from severe shortness of breath on exertion for years and also from severe attacks of pain that might come on at any time and pass down the arm. These might be accompanied by faintness. In addition, she had a persistent left-sided ache which was worse after exertion and also passed down the left arm. On examination there was mitral stenosis with a regular rhythm.

Case 7. A woman, aged 32, had suffered for two years from pain in the left side of the chest, which was worse on exertion and was accompanied by palpitation and a feeling of weakness. On examination there was no abnormality except for a systolic murmur at the apex, conducted to the pulmonary base.

PATIENTS WITH ANGINA OF EFFORT

Case 8. A man of 54 had for 10 years suffered on rare occasions from a slight pain, central in position and substernal. This came on only after digging, sawing, or similar strenuous exertion. He had been examined several times and had been told that he had heart disease, which was probably due to rheumatic fever in the past. A year before he was first seen he began to get pain frequently

on exertion, which would go with resting and was quantitative to the amount of exertion. It was never present at rest. On examination the apex beat was just outside the mid-clavicular line and was forcible. A harsh loud systolic murmur was present at the aortic base, with a systolic thrill, and the murmur was also heard at the apex. The blood pressure was 150/110. He remained under observation for two years before he was referred for psychological treatment.

Case 9. A man of 65 had suffered for two years from a retrosternal pain that only came on as he walked and was proportional in its severity to the amount of walking. It was not increased by emotion, but was always accentuated by hills. On examination there was no increase in the blood pressure, but the apex beat was slightly displaced to the left, the heart/chest ratio being 14/27 cm. The electrocardiogram showed left-sided preponderance and some notching in the R wave in lead II. (See later.)

Case 10. A man of 49 had had pain in the chest on exertion for two years ; it was central in position but did not radiate to the arms. This was quantitative to the amount of exertion but was also brought on by excitement. Six weeks before he had had a severe attack of pain on getting out of bed, upon which he fainted. It lasted on and off severely for a week. Since then he had been slowly improving. He was then watched for a period of two months, during which the pain remained unchanged in degree. On examination he had severe hyperpiesis, 235/140 mm., the heart showed no clinical enlargement and the sounds were normal. The electrocardiogram showed no abnormality. (See later.)

TABLE II

PATIENTS WITH ANGINA OF EFFORT

Case number	Age and Sex	Diagnosis	Duration of Treatment		Result of Treatment		Follow-up	
			Physical (in years)	Psychological (in months)	Pain	Psychological symptoms	Duration (in months)	Results
8	54, M	Aortic stenosis, hyperpiesis, anxiety state	4	4	Lost	Improved	18	No pain for 6 months ; then relapse with erysipelas
9	65, M	Reactive depression	3	3	Lost	Improved	12	No pain for 6 months ; some recurrence, but slighter and less frequent
10	49, M	Hyperpiesis, anxiety state	2	10	Much improved	Improved	7	Occasional slight pain ; other symptoms better
11	51, M	Anxiety state	2	2	Improved	Improved	3	Much improved
12	49, M	Hyperpiesis	13	8	No change	No change	3	Unchanged

Case 11. A man of 51 had had pain that was quantitative to exertion for two months. The onset had been gradual and the pain was not present at rest. The pain was of a squeezing nature and radiated down to both forearms. It was worse on walking uphill and caused him to stop and might last up to two minutes. He had had two slight attacks in bed. The electrocardiogram showed flattening of the T wave in leads I and IV. During a period of four months, while under treatment as an out-patient, his symptoms became slowly worse. He was, therefore, referred for psychological treatment.

Case 12. A man of 49 had felt slight pain on the left side of the chest for sixteen years. This was at first of the functional type, being left-sided, radiating to the left arm and elbow, but having no relation to exertion or emotion. It might persist for variable lengths of time up to several hours and was not relieved by nitroglycerine. One year previous to examination he had an attack of angina of effort, the pain now being strictly quantitative to exertion and disappearing when exertion slowed down or ceased. Since then he has had angina of effort of a moderate degree. Six years before his systolic blood pressure was 150, but two years before it had risen to 210/110. On examination the heart showed slight enlargement and there was a systolic murmur at the apex. The blood pressure was 210/138. The electrocardiogram was of the low voltage type and showed some slurring and widening of the QRS complex.

Nature of Psychological Treatment

Short methods of treatment have been employed in these twelve patients. Each was seen three times a week for an hour. With a few exceptions, the treatment was limited to 60 hours. In some cases, superficial discussion of the current conflict was found to be sufficient to relieve the complaint. In most cases, however, the treatment was conducted along analytical lines, i.e., by free association while lying relaxed on a couch. The aim of such treatment is to help the patient to bring out and to face attitudes, previously unrecognized, which are often strongly emotional. As serious cardiac disorders were present in many of the patients, severe emotional shocks were avoided by keeping interpretation on a comparatively superficial level.

Co-operative patients with a mild or moderate psychological disorder were preferably taken on for treatment. Advanced age, complaints of very long standing, a low standard of intelligence, as well as evidence of a very severe psychological disorder were generally considered as contra-indications. In the group with functional cardiac pain, the psychological diagnosis was labelled as an anxiety state in three patients, as conversion hysteria in three, and as a character disorder in one. Four patients with angina of effort suffered from anxiety states, in two of them with a pronounced obsessional background, and one patient from a reactive depression.

Results on Discharge and After Follow-up

1. *Functional Type of Pain*

There will be very little argument about the indication for psychotherapy in patients with cardiac pain of the functional type. Most cardiologists, in

these cases, employ some form of psychotherapy in an open or concealed form. A glance at Table I shows that, before the beginning of psychological treatment, the patients had received physical treatment of about two or three years—in one case for ten years—without much benefit. The results of psychological treatment can be summarized as follows.

(a) *Cardiac Pain.* After an average of four months of psychological treatment, six of the seven patients had lost their cardiac pain.

(b) *Occupational Efficiency.* Three patients who were incapacitated by their complaint, returned to work at the end of the treatment.

(c) *Psychological Complaints.* Their nervous symptoms, e.g., anxiety, shaking fits, etc., were improved or completely relieved.

(d) *Follow-up.* In four cases this covered a year or more, and three patients kept up their recovery over the whole period of observation. One was completely restored for six months, but had a relapse in connection with decompensation of the heart ; another, after six months of apparent health, died of acute uræmia. In one, who did very well under treatment, the follow-up is too short. The only patient who did not respond improved during a further course of treatment by Dr. Crichton-Miller, under evipan administration.

2. *Angina of Effort*

Five patients with angina of effort (Table II), after physical treatment without much avail over several years, were taken on for psychological treatment. The results can be summarized as follows.

(a) *Cardiac Pain.* Two of them, who before treatment were hardly able to walk 100 yards without an attack, were completely relieved from pain at the end of the treatment ; two were improved ; and one was not amenable to treatment.

(b) *Occupational Efficiency.* In two patients occupational efficiency was restored under treatment.

(c) *Psychological Complaints.* With one exception the patients reported an improvement of their nervous symptoms.

(d) *Follow-up.* This, as should be anticipated, is less satisfactory than in the functional group. The two patients that lost their pain under treatment remained free for six months ; afterwards, one relapsed in connection with erysipelas and the other noted a slight return of pain. " I get the pain only occasionally," he says in a letter, " instead of frequently, and the pain is less when it does occur than it was formerly." The two improved patients kept up their improvement. One did not respond to psychological treatment.

Illustrative Cases

The points at issue are best illustrated by some typical instances.

Case 1. A big, loquacious, simple-minded man, aged 54, had suffered from attacks of cardiac pain for over three years—" like a knife stabbing." The pain extended along the left arm and was brought on by hard work, excitement, and worry. He was admitted to a hospital, where he was told by one of the physicians that it was angina

pectoris and that he should avoid any exertion. Since then he had been out of work, resting at home ; he could not walk 100 yards without the pain starting. For the past twelve months he had been sitting in a chair, hardly ever leaving his ground floor room. The physical diagnosis was functional type of cardiac pain.

The youngest of nine children, he was spoilt and pampered as a child. He was his mother's special favourite and from early childhood was over attached to her. He declined to marry as long as she lived, although she urged him to do so. After her death, when he was 28, he had a serious nervous breakdown, but married a year later.

He had worked as a parquet-floor layer. When 47 he began to worry more about his work, because there was a new manager who wanted the work to be done more cheaply. As a foreman with a higher wage, he had to work harder than the others and he worried day and night about getting the sack. Very often he could not sleep, and developed headache, giddiness, and morbid fears of crowds and enclosed spaces. " I worried until I collapsed." About two years ago he collapsed at work and immediately afterwards his attacks of heart pain started.

After four months' psychological treatment, his pain disappeared and he returned to his work. Since then he has been free from any complaints. " I walk and enjoy it. My wife grumbles that I walk too quick. I sleep well and awake refreshed. There's a brighter atmosphere all round."

Case 9. A retired schoolmaster, aged 65, a pleasant, friendly, compliant Lancashire man, began to have typical attacks of angina of effort three years ago. He was seen by various heart specialists and told to avoid any exertion. He was unable to walk any distance without attacks of cardiac pain setting in. He had worked his way up from great poverty to be an assistant schoolmaster. In 1928, after quite a successful career, he had to leave as a newly appointed headmaster insisted on his dismissal. After that a hard struggle began ; being advanced in age, he only got temporary posts and eventually, three years ago, found it impossible to get a job at all ; his savings were used up and, unable to support himself, he became entirely dependent on his son. About this time his attacks of angina of effort started.

Superficial discussion of his conflicts was sufficient to relieve his complaints. For six months he remained free from pain, after which slight occasional pain returned.

Case 10. A silversmith, aged 49, attended hospital because of violent attacks of pain in the middle of the chest. He had had these for over two years, brought on by heavy meals, excitement, or the slightest exertion. The diagnosis was angina of effort and hyperpiesis.

He was a courteous, unassuming, little man, self-conscious and blushing easily ; in contrast to his docile and almost timorous behaviour, however, he was harassed by what he called aggressive thoughts. He had impulses to punch people or to spit at them or to cut his wife's throat and, although he never did, was haunted by the fear that he might give way to these impulses and might be locked up and hanged. Further exploration revealed that he had been a most aggressive, troublesome baby but his aggressiveness had been nipped in the bud by a stern, dogmatic father. Rarely, and then only at the peak of resentment, did the patient display aggressiveness in any shape or form.

All through his life he has been rather touchy about any encroachment on his independence, and never liked to be dictated to by anybody. Frequent arguments with his wife arose because he rather emphatically insisted on being " governor in the house." In contrast to this, in recent years he has developed a fear of being thought effeminate and an urge to touch the private parts of a man. Any innuendo in this direction or even discussion of the subject of homosexuality made him blush violently. During the past two years he has been impotent and, in fact, owing to a pronounced fear of going out and of collapse, he has got into a state of complete dependence on his wife. He gave up his job, his wife kept and nursed him and he would never leave the house unless she accompanied him.

Investigation revealed that as the eldest of nine children he had been his mother's

favourite and, whereas he was over-attached to her, he was scared of, and strongly resentful of, his father. One incident, which he said he had never got over, stood out in his memory. His mother was being confined when he was five or six years old ; he had heard her groaning and wanted to find out why she was doing it but his father pushed him out of the room.

At about 18 he started to masturbate and about the same time to drink. His father was against his drinking and said that he would have to pay for it. After some months he broke down completely ; he cried incessantly, was afraid to go out and developed a fear of insanity. This condition passed off after several weeks. Twelve years ago he had a second nervous breakdown. His fears of going out and of insanity returned and he refrained from sexual intercourse for two years, as he thought this might drive him mad.

Two years ago his mother died and her death initiated his third nervous breakdown. Since then the attacks of cardiac pain, the impotence, and various psychological complaints have developed. " I still want to hang on to my mother and to ask her if to do something will be all right."

As the patient faced up to his previously unrecognized attitudes, the attacks of cardiac pain gradually got less frequent and less severe. He returned to work, his potency was restored, and his nervous symptoms have greatly improved.

Comments and Conclusions

The data obtained confirm the view put forward previously, that in cases of functional cardiac pain the pain is nearly always due to transformed anxiety arising from a conflict, unusual in intensity and abnormal in type, between menace to vital feelings and existence on the one side and self-preservation and self-assertion on the other. It is almost a truism to state that those harassed by anxiety are more apt than others to develop cardiac pain, if for some reason or other they are affected by some cardiac disorder. Both in cardiac pain of the functional type and in true angina of effort, relief of underlying anxiety by psychological treatment results in improvement or loss of cardiac pain.

As should be expected, psychotherapy has very little or no effect on the organic cardiovascular disease, the blood pressure and cardiac condition remaining unchanged ; it could, therefore, be objected that removal of pain, as it removes the essential warning not to overdo physical exertion, may be injurious. However, none of the patients with angina of effort died during the prolonged follow-up period and, in fact, as the anginal attacks may in part be due to spasm of the coronary arteries, removal of these attacks may result in an improved circulation in the coronary system.

Summing up, it has been suggested that patients with the functional type of pain and certain patients with angina of effort derive benefit from psychological treatment. The diagnosis of cardiac pain of the functional type is an indication for psychological investigation and possibly for systematic psychotherapy. Only in certain cases of angina of effort, carefully selected as in the cases quoted because of a prominence of emotional elements, is an attempt at psychotherapy justified.

The research was carried out during the tenure of a Research Fellowship granted by the Sir Halley Stewart Trust to one of us (E. W.) and we are very much indebted to the Trust. Our thanks are also due to the Medical Research Council for their grant towards some of the expenses of this investigation.

ANALYSIS OF FIFTY NORMAL ELECTROCARDIOGRAMS INCLUDING LEAD IV

BY

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An analysis of the electrocardiograms of 50 normal women students between the ages of 20 and 27, attending the Royal Free Hospital, is given. Originally the records of 100 students were taken, but later it was decided to select 50 that showed a normal relation between weight and height and were physically fit. Special attention was directed to lead IV and its possible relations to the three standard leads. In all our work lead IV R has been used, i.e. left arm electrode at the extreme outer border of the apex beat as the exploratory electrode and right arm electrode as the distal indifferent electrode, this following the recommendations of the joint report of the Cardiac Society of Great Britain and Ireland and the American Heart Association in 1938.

It is proposed to analyse the duration, form, and amplitude of each wave. A number of tables, frequency curves, percentage relations, and mean values have been constructed for these in each lead ; only a few of them have been selected for reproduction in the text.

THE P WAVE

All the measurements given in the text have been made according to the standard method except where otherwise stated. The earliest accurate measurements of the amplitude and duration of the P wave were made by Lewis and Gilder (1912) and by Goodall and Richards (1914).

Form. Table I shows that this is very variable, the round and pointed forms being most prevalent. The large preponderance of the pointed shape in lead II and the great variation in lead III are also noticeable. Bifid waves were found only in lead I. In two records the form was not the same in each cycle, varying between the pointed and round shape. We cannot give a satisfactory explanation of the factors responsible for the variation from cycle to cycle, and one must assume that in every cycle the excitation wave follows a slightly different path. At the same time the summation of the electrical activity of both auricles is not symmetrical and smooth. As a result the P wave curve changes its form from round to notched, bifid, or pointed.

TABLE I

FORM OF P WAVE IN 50 CASES (PERCENTAGES)

Form	Lead I	Lead II	Lead III	Lead IV
Round	36	24	32	56
Pointed	50	70	38	40
Round or pointed ..	—	6	8	2
Inverted	—	—	12	2
Bifid or flat	14	—	10	—

Shipley and Hallaran (1936), in an analysis of the electrocardiograms of 200 normal men and women, recorded smooth and round P waves in 67 per cent. and pointed in 33 per cent. Notching was present in 30 per cent., but only in one record was it found in all leads. P was inverted in 5 per cent. of their records, but only in lead III. A diphasic P was met once in lead II and 32 times in lead III. When P was inverted, T was also inverted; and when P was diphasic in lead III, T was also diphasic. We found a similar relationship, but in one record P was inverted in lead IV and T was upright. In subsequent tracings inversion of P was noted in other leads or cycles, whereas in lead IV the auricular deflection was upright. This was a case of wandering pace maker. The association of the amplitude of P greater than 2 mm. and notching was not met with in our cases, nor in those recorded by Shipley and Hallaran, and we agree with them and others that this association is one of the signs of mitral stenosis.

Amplitude. Originally Lewis and Gilder gave the following values for the P wave deflection in 52 healthy subjects; lead I=0·52 mm., lead II=1·16 mm., and lead III=0·81 mm. More recently Burnett and Taylor (1936) gave an analysis of 1276 electrocardiograms taken from 167 children, aged 3 weeks to 12 years, of whom 85 were boys and 82 girls. The amplitude was higher than in adults (upper limit 2·5 mm. and lower limit 0·5 mm.). The girls showed a higher amplitude than the boys, but after the age of ten there was less variation in all leads. In résumé the authors state that P showed higher and lower deflections in children than in adults, more frequently high in girls than in boys, but that the average did not show any notable departure from the average value found in the adult.

Shipley and Hallaran give the average amplitude of the P wave for men as 1·41 mm., and for women as 1·30 mm. in lead II, which showed the greatest deflection of P in 90 per cent.

In comparing the average value of our 50 students, we found much higher figures than those given by previous investigators (see Table II). The mean value of P in the four leads was 1·74 mm. ; and the greatest value, in lead II, 2·3 mm. The maximum and minimum deflections of P in our records were 5 mm. and 0·5 mm. This shows that large P waves occur quite often and have no abnormal significance. The highest average deflection was found in lead II, and the next in lead IV.

TABLE II

AMPLITUDE OF P WAVE IN 50 CASES (PERCENTAGES)

Range of Amplitude in mm.	Lead I	Lead II	Lead III	Lead IV
0–1	6	—	24	2
1–2	72	36	48	58
2–3	20	38	26	34
3–4	2	18	2	6
4–5	—	8	—	—

Duration. Our measurements for the duration of the P wave fit in to some extent with those of other investigators and with those of Shipley and Hallaran, who give the value of 0·08–0·12 sec. for the duration of P for men and women alike. Their average is 0·09 sec. and the longest duration 0·12 sec. The average values found by us were 0·08 sec. in each lead, except in lead I where it was 0·07 sec.; and the mean value for the four leads was 0·076 sec. This value is lower than that reported by the above mentioned investigators, and our view is that in young women the duration tends to be shorter than in men. From our measurements it appears that there is no definite relation between the amplitude and the duration of the P wave.

THE P–R INTERVAL

P–Q Duration. This was measured from the end of P to the Q deflection The mean value for each lead was 0·06 sec., except in lead III where it was 0·07 sec.

The mean value for the four leads was 0·064 sec. The longest duration was in lead III, 14 per cent. being between 0·09 and 0·12 sec., and 70 per cent. between 0·06 and 0·09 against the 50 per cent. in the other leads. In comparison with the values exhibited by the normal heart, cases of mitral stenosis tend to show a short P–Q duration.

P–R Interval. The value of the P–R interval 0·13–0·21 sec. established by

TABLE III

DURATION OF P–R INTERVAL IN 50 CASES (PERCENTAGES)

Range of duration in seconds	Lead I	Lead II	Lead III	Lead IV
0·09–0·12	22	4	6	6
0·12–0·15	58	50	32	54
0·15–0·18	16	42	52	38
0·18–0·21	2	4	6	2
Mean value (seconds) ..	0·13	0·14	0·15	0·14

Lewis and Gilder (1912) has been adopted beyond criticism as a normal range. Lewis showed that for cats it is 0·06–0·08 sec., and for dogs 0·08–0·10 sec. Paul

White in his book gives the normal value for adults 0·20 sec. (average 0·16 sec.) and for infancy and childhood 0·08–0·18 sec. (average 0·125 sec.). The results of our analysis of P–R are reproduced in Table III, and the frequency curves in Fig. 1. The range of duration was between 0·09 and 0·21 sec. In lead I most cases fell within the range 0·12–0·15 sec., with a large number of small duration,

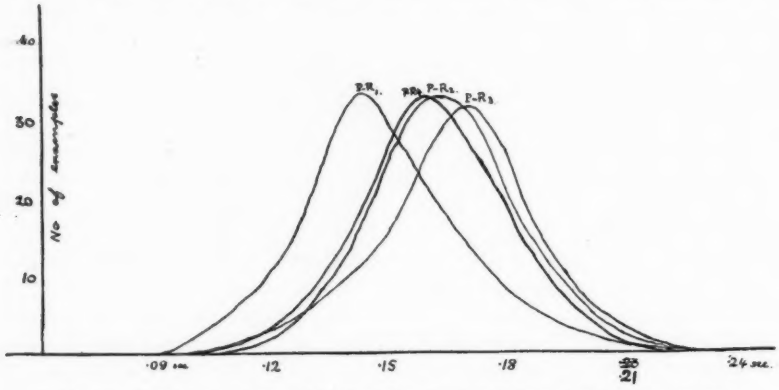

FIG. 1.—Frequency curves of the duration of the P–R interval in the four leads.

0·09–0·12 sec. In the other three leads the greatest number of cases were between 0·12–0·18 sec.

THE QRS COMPLEX

The most variable part of the QRS complex and that on which a considerable number of investigations has been published, especially in relation to coronary disease, is the initial ventricular deflection, the Q wave. The first wave of the ventricular complex is designated as Q by Einthoven, if it points down, and as R if it points upwards. S denotes the downwards wave that comes after the upward R, and where there is no upward wave the downward wave is designated as S. Lewis in his book (1925) states that Q is " beyond question a ventricular event, occurring as it does in curves of complete dissociation of auricle and ventricle as part of ventricular complex, as was first pointed out by Einthoven." If QRS is inverted, as in dextrocardia or in abnormal axis deviation, Q and S will also be inverted and point upwards. Besides that, as we shall see, there are normal curves in which the initial ventricular deflection is such that it is difficult to distinguish Q and whether it points downwards or upwards. Sometimes Q is absent or flat or represented as a thickening at the beginning of the R wave, in which case it is called fused. Finally Q may be replaced by an initial diphasic phase at the beginning of the R wave. The electrocardiograms, Fig. 2, A and B, are examples of " inverted " Q according to some American authors ; Fig. 2C is an example of Q fused to R, or flat ; and Fig. 2D is an example of " diphasic " Q.

Paul White (1937) states that Q is usually absent in lead II or may be a

short point, projecting 1–2 mm. below the base line, and that in infants and young children it may form a more appreciable part of the QRS complex being as much as 3–4 mm. in amplitude. In lead I, according to him, the QRS complex is such that it is often impossible to tell whether we are dealing with an upright Q, an inverted R, or an upright S, and such variations certainly occur in some cases.

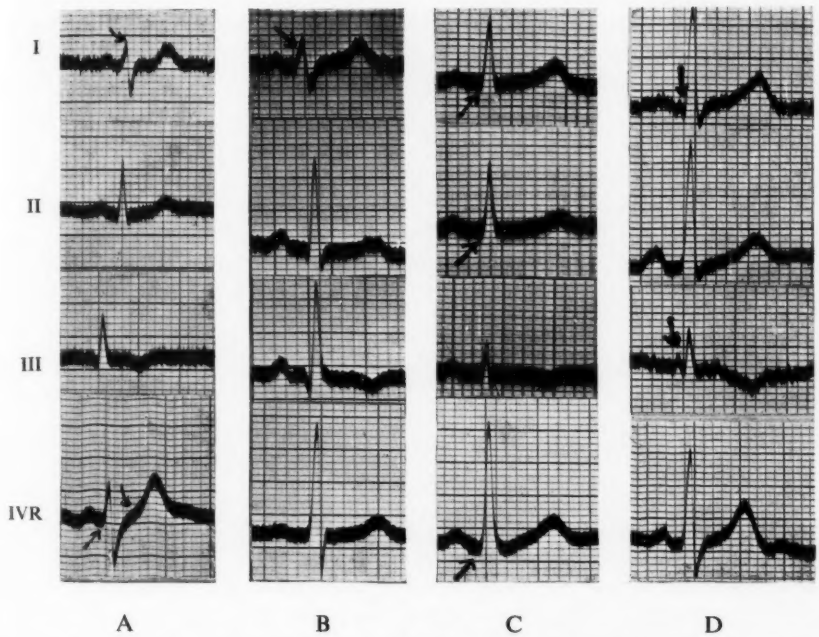

FIG. 2.—Cardiograms selected to show different types of deflections discussed in the text : (A) and (B) show inverted Q in lead I ; (C) shows Q fused to R ; (D) shows diphasic variation of Q in leads I and III.

Pardee (1933) has drawn attention to a deep Q_3 as an indication of myocardial disease. Kossman, Shearer, and Texon (1938) affirm that normal subjects with a deep Q_3 rarely show the other criteria of Pardee. In a combined series of reports from Lewis and Gilder, Cohn, Master, Pardee, and Edeiken and Walwerts a deep Q_3, according to the above criteria, was found twice in the electrocardiograms of 1102 young men, including 116 normal athletes.

We have investigated Q_3 according to Pardee's criteria in all our cases. A deep Q_3 was of frequent occurrence and was more frequent in young women and children than in adult males. But in no electrocardiogram did we find the Pardee criteria followed, except in one (Fig. 3C). It is from a woman, 21 years of age, who shows clinically no heart abnormality and is in perfect health. There is a deep Q_3, of over 4 mm., which is more than 25 per cent. of the

largest QRS complex in any lead. There is also a conspicuous Q in leads I and II and low voltage in lead IV. The arrow in the record is pointing to show " fusion " between S and R in lead III, according to the interpretation of Hurxthal and others. There is also an inverted or isoelectric P wave and an inverted T in lead III. We consider this electrocardiogram is a rarity because it follows Pardee's criteria although it is from a normal person.

We feel that unless we know all the possible variations of Q in normal persons it is difficult to accept with confidence its diagnostic value as suggested by the American investigators in coronary infarct. Table IV shows the analysis of the form of Q deflection.

TABLE IV

FORM OF Q WAVE IN 50 CASES (PERCENTAGES)

Form	Lead I	Lead II	Lead III	Lead IV
Down (or down -fused or -diphasic)	52	64	50	24
Upright * (or upright-fused) ..	4	—	16	4
Flat * (or flat -fused or -diphasic)	44	36	34	72

* The terms upright, flat, fused, or diphasic, are adopted from the works of certain American authors, e.g. Hurxthal, but their acceptance is not yet general.

Recently Kossman, Shearer, and Texon (1938) have reported the detailed study of the incidence and quantitative relationship of the Q deflection of the three standard leads of the electrocardiograms of 178 normal subjects in order to find a standard for comparison for any type of heart disease. In either the sitting or recumbent position and during either phase of respiration, 40 per cent. showed a Q deflection in lead I, 60 per cent. in leads II or III, and 40 per cent. (or slightly less) in both leads II and III.

R Deflection. The R wave follows immediately the initial ventricular deflection. According to the general view it is composed of two projections, an upright which starts from Q and a downwards which ends in S, the final deflection. The amplitude of R in our curves was measured from the isoelectric line to the summit, and the slight or deep downwards deflections produced by Q or S were ignored. However, in some records especially in lead III, R is diphasic or may take the shape of M or W. The R deflection is considered diphasic when the projection, instead of starting from a downward or flat Q, starts from an upright (inverted Q) and finally goes downwards to a deep S wave.

The diphasic R should not be confused with an inverted R met with in left or right preponderance. In this case the R deflection starts from the isoelectric line from an inverted Q, projects downwards, and then ascends back to the isoelectric line to an inverted or fused S wave. A diphasic R has a positive phase which is above the isoelectric line and a negative phase which is underneath

the isoelectric line. This interpretation is not generally accepted, but we consider it necessary. In some records the positive part of a diphasic R is very small on account of a big initial Q inversion (see Fig. 2B). In other records it starts from a smaller inverted Q and descends to a deep S (see Fig. 2A, leads I and IV). However, it is sometimes very difficult to differentiate between a diphasic R wave and an inverted Q wave. For example, in Fig. 3A in

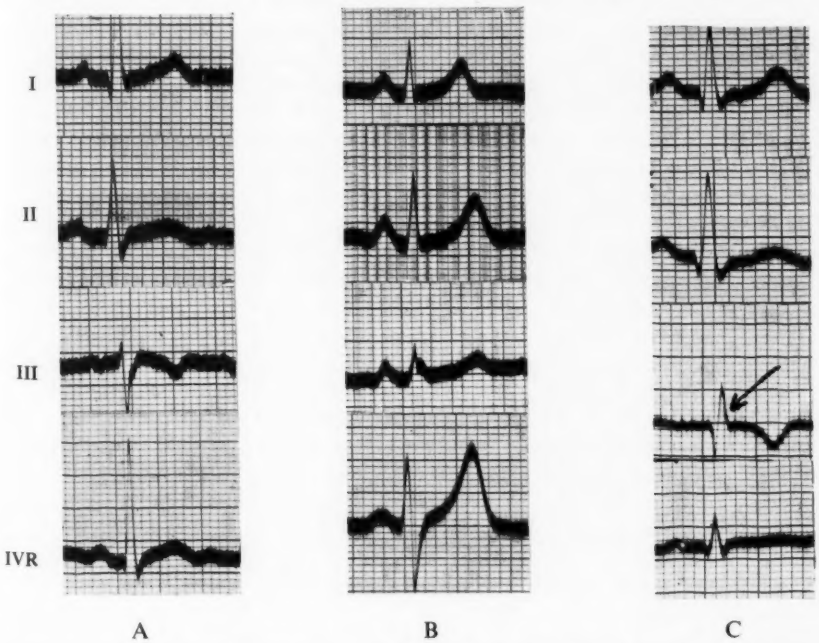

FIG. 3.—(A) Upright Q in lead III : (B) S fused in lead III when Q is fused or upright in lead I : (C) Example of Pardee criteria found in a normal subject.

lead III there is an upright Q and an inverted R, but there are no other signs of left preponderance. The R wave in lead II is not diphasic and there is a medium projection of R in lead I. The record is from a young student who is a good athlete. All that can be said is that she has a well developed left ventricle.

The relation between Q in lead I and S in lead III is considered significant. In our records it was found that almost always when Q_1 was upright or fused, S_3 was fused (Figs. 2, A and B, and 3B). An exception to this rule was observed in only 3 out of 50 electrocardiograms. It does not follow, however, that when S_3 is fused Q_1 is also fused. In 20 records out of 50, S_3 was fused while Q_1 was not.

According to Hurxthal (1933), in left axis deviation, Q_1 points down markedly and Q_3 shows a distinct upright deflection. In right axis deviation Q_3 points downwards (Q_1 being upright) and, if R_1 is slightly upwards, slurring of the origin of R will be found. One can reasonably assume this to be a

fusion of upright Q and R. Also he states that if the law of Einthoven can be applied to separate phases of QRS this will be helpful for correct identification of a deflection, as very often somatic tremor or other irregularities or abnormalities make it difficult to separate various components.

Paul White gives as limits for the R deflection in normal adults 5–35 mm. and in infants 5–10 mm. Pardee sets the lower limit at 7 mm. and by most authors smaller deflections than this are considered as low. Steuer (1933), taking 7 mm. as the lower limit reviews 50 cases with low voltage, all having had post-mortem examinations. All showed severe myocardial lesions due to coronary disease, tertiary syphilis, rheumatic heart disease, or nephro-sclerosis, or in a few cases miscellaneous causes such as acute or chronic infections, cancer, etc. Shipley and Hallaran record low voltage electrocardiograms under 7 mm. in three apparently normal subjects. In the Burnett and Taylor (1936) series, the results were : 55 cases, 17 mm. or over ; 44. 7 mm. or below ; 4, 3 mm. or below.

We accept the view that a deflection of R under 5 mm. in all leads (including lead IV) is rare and is a sign of serious myocardial damage. Below are recorded the values found in our 50 cases analysed according to leads :

TABLE V

SIZE OF R WAVE IN 50 CASES (PERCENTAGES)

Size of Deflection	Lead I	Lead II	Lead III	Lead IV
5–7 mm.	24	2	18	2
7–17 mm.	72	76	56	44
17–31 mm.	4	22	2	44
Mean value (mm.) ..	9·8	13·5	6·5	1·74

In 12 records the deflection of R in lead III was under 5 mm., 2 records being just under 2 mm.; in 6 it was between 3–4 mm., and in 4 between 4–5 mm. The maximum deflection of 31 mm. was found twice in lead IV. No slurring or notching was seen in our series of cases.

Duration of QRS. The earliest work on QRS duration was done by Lewis and Gilder (1912), who state that the normal duration must not be over 0·10 sec. We are reproducing here the values for QRS duration according to different investigators quoted from the paper of McGinn and Paul White (1933). Ferguson and O'Connor (1926) in 1812 young people report a duration of over 0·10 sec. only in 2 records ; Jensen, Smith, and Cartwright (1932), found a duration of 0·06–0·08 sec. in 50 patients. Seham (1921) reports the following values in children : birth to one year, 0·036 sec. ; one to five years, 0·05 sec. ; over five years, 0·07 sec. Lincoln and Nicolson (1928) give 0·06 in 222 normal school children. McGinn and Paul White, using the Lucas comparator described in detail by Lewis (1925), find the following figures : 50 males, average 0·083

(66 per cent. over 0·08 sec.) ; 50 females, average 0·072 (20 per cent. only over 0·08 sec.). The average for all cases and all ages was 0·078 sec. Eleven persons were tall, 10 of whom had a duration of QRS more than 0·083 sec. In 50 normal children under 12 years, 26 boys and 24 girls, the average QRS duration was 0·072 sec. The duration tends to be slightly longer in boys than in girls. Shipley and Hallaran (1936) found a smaller difference between the average QRS duration in males (0·087) and in females (0·085).

The values of the QRS interval found in our 50 normal cases differ to some extent from those reported by previous authors. In general the duration is shorter. The mean values were 0·06 sec. in the three limb leads and 0·05 sec. in lead IV. The shortest duration was 0·03 sec. and the longest 0·09 sec., both in lead III. Although lead IV shows the largest voltage, the QRS duration was the shortest in this lead. The measurements were made from Q or the beginning of the ascending spike of R to the beginning of S or in absence of S to the fusion of R and S. If Q and S deflection were " fused " with R or absent, the measurements were made at the level of the fused part on the base line. When R was diphasic the measurements were made from Q to the tip of the lower deflection of S.

It was thought that one of the reasons for the short duration of QRS was the fast rate found in most of our records, but no relationship between the duration of QRS and the duration of whole cycle could be established.

S-Wave. The variations of S are less frequent than those manifested by Q. There appears to be no definite relation between Q and S with regard to their form, nor is there at present any satisfactory explanation of the variations of the form of the S wave.

Amplitude. The S deflection is in general more conspicuous than Q and is greatest in lead IV, in contrast with Q which is smallest in this lead. The mean values that were found for S are shown in the first column following :

Lead	mm.	mm.
I	1·08	2·06
II	0·79	2·23
III	0·08	1·73
IV	3·28	—

The figures in the second column show the average values found by Lewis in normal adults. Burnett and Taylor (1936) report that S is deeper in children than in adults and that it decreases in size with age in all leads.

The Second Ventricular Deflection or T Wave

We have analysed here separately the S–T segment (the interval between S to the beginning of T), the T wave itself, and the classical S–T duration. According to Lewis (1925, p. 119) there is always a definite relation between the direction of T and the direction of either Q or S, usually the latter. An upright T is always preceded by a downwards S, and if T is inverted S is usually upright, but if not, Q is upright. Since Lewis's work many investigations have been published

on the significance of the T wave and its relation to the initial deflections of the ventricular complex. According to Craib's (1930) conception there is no constant relationship between the direction of the T deflection and the direction of any deflection of the initial group, because the QRS deflection is recorded before there is any material movement of the myocardium, whereas the end deflection of T is recorded when there is a gross displacement of the myocardium. He held the view that the human electrocardiogram is composed of an initial quick deflection recorded before contraction and a prolonged end deflection recorded when the whole ventricular mass is in contraction. Theoretically each deflection is the result of multiple simultaneous contributions from all parts of the heart, and only the part of the summation that is in the same direction as the lead is recorded. Craib explains the electrical events recorded during ventricular activity by referring to his mathematical hypothesis of doublets, which is based on the view that currents flowing about active tissue must flow between anodes and cathodes localized at the affected part of the tissue.

S–T segment (*S to beginning of T*). Shipley and Hallaran (1936) point out that the level between QRS and T is influenced not only by the ventricular events but also by the so-called auricular T wave. We have measured in our records the deviation of the S–T segment from the P–R level. The S–T segment was most often raised in leads I and II, depressed in lead III, and slightly raised in lead IV. We cannot, however, draw a definite conclusion at present as we found difficulty in the identification of the auricular T effect.

Duration. On recording the duration of the S–T segment great difficulties are met with on account of the variation of form. The greatest value found was 0·24 sec. in lead III, and, as already stated, the segment was absent in a great number of records. The average values were as follows : 0·11 sec. in leads I and II, 0·13 sec. in lead III, and 0·10 sec. in lead IV.

The form and amplitude of the T wave. This varies with age. Burnett and Taylor (1936) in 167 healthy infants and children report well-defined T waves in leads I and II, and low voltage T waves in lead III in infants three weeks old. In children, T_1 is higher than the adult standard of 5 mm., T_2 reaches an amplitude of 8 mm., while T_3 is found to follow the adult type.

The authors describe also the susceptibility to external influences of T in childhood. In several records T_3 becomes inverted when the child changes from the recumbent to the sitting position. This appears to be due to some shift to the right, since mediastinal structures are very flexible in childhood. In adults it has a greater stability than in childhood, but this varies with the sex. In women, the T wave, especially in lead III, is less stable and shows a greater variation than in males. The round form T was more frequent in leads I and II, while the pointed form was more frequent in lead IV (62 per cent.).

The characteristic feature of T in some leads is the immediate take off from the R–S base with the rapid ascending peak and the abrupt drop. This type was more frequently met with in lead IV. We feel that this should not be interpreted as an absence of the S–T segment, but as a fusion between S–T and the ascending part of T. The evidence pointing in this direction is the existence of an increased time duration for T when the S–T segment is abrupt or fused.

This association was found 21 times in lead IV, 6 times in lead I, and 3 times in lead II.

Inversion of T was found most often in lead III (46 per cent.). The view of Lewis, that when T_3 is inverted, S or occasionally other deflections of QRS point in the opposite direction to T, is fully confirmed by our observations. Out of 23 records in which T_3 was inverted: S_3 was fused and upright in 12 records ; upright in 2 ; and flat in 3 records ; in the remaining 6 S_3 was downwards, with R inverted and Q upright in 4 records and with Q upright in 2 records.

As already stated the largest amplitude of T was found in lead IV, and an analysis of the deflection in all leads is reproduced in Table VI and in Fig. 4.

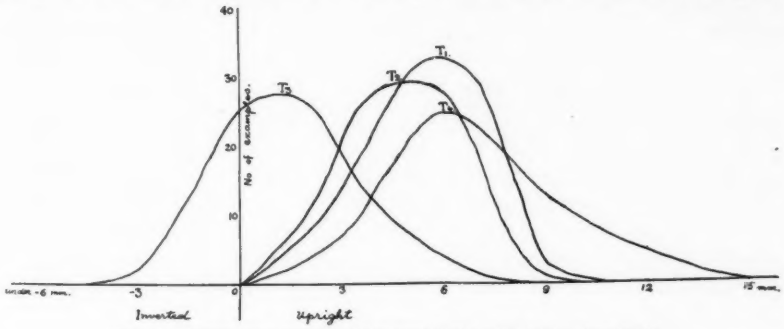

FIG. 4.—Frequency curves of the amplitude of T in the four leads.

The average values of the amplitude are also as given in the table. It is interesting to note that the average value for T in lead I had a slightly larger value than in lead II in our records. This suggests two explanations :

1. There is a slight preponderance of the right over the left heart, in accordance with Lewis's bicardiogram hypothesis with regard to the summation of the events in both ventricles.

2. In young women the anatomical position of the heart and the axis of the direction of the change of potential are such, that in lead I the potential recorded for the T wave is slightly larger in certain cases than that recorded for the T wave in lead II.

This may explain also the large proportion of inversion (46 per cent.) and

TABLE VI

AMPLITUDE OF T IN 50 CASES (PERCENTAGES)

Range of amplitude in mm.	Lead I	Lead II	Lead III	Lead IV
−6 to −3	—	—	4	—
−3 to 0	—	—	50	—
0 to +3	28	42	38	14
+3 to +6	66	56	8	50
+6 to +9	6	2	—	26
+9 to +12	—	—	—	10
Average amplitude (mm.)	+3·23	+3·22	−0·74	+5·07

isoelectric T in lead III (30 per cent.). The S deflection shows also a larger average value in lead I than in lead II. In contrast with the T and S deflections the Q and R deflections show larger values for lead II than for lead I.

Duration of T. No relation was found between the amplitude of the T deflection and the duration. In Table VII below is reproduced the analysis of the T wave duration.

S–T Duration. The S–T segment and T wave added together form the S–T duration—the second part of the ventricular deflection. The range of values found in our records was 0·16–0·36 sec., the minimum being found in 3 records in lead III, and the maximum in 6 records in lead I, 3 records in lead II, 2 records in lead IV and 1 record in lead III. The average values were : lead I, 0·28 sec. ; lead II, 0·27 sec. ; lead III, 0·25 sec. ; and in lead IV, 0·28 sec.

TABLE VII

DURATION OF T IN 50 CASES (PERCENTAGES)

Range of duration in seconds	Lead I	Lead II	Lead III *	Lead IV
0·04–0·08	—	—	6	—
0·08–0·12	6	—	28	—
0·12–0·16	36	26	28	14
0·16–0·20	40	68	6	60
0·20–0·24	16	6	4	22
0·24–0·28	2	—	—	2
Mean value (seconds)	0·16	0·16	0·12	0·17

* T was isoelectric in 14 records in lead III, and in one record in lead IV, and therefore not measured.

The values found by us in 50 normal records are in general smaller than those given for adults in most books on electrocardiograms.

SUMMARY

An analysis of 50 normal electrocardiograms has been given. The form, amplitude, and duration of each deflection have been studied in the light of classical and recent investigations. The three standard leads and lead IV R, drawn according to the calculated mean values, are reproduced in Fig. 5. The

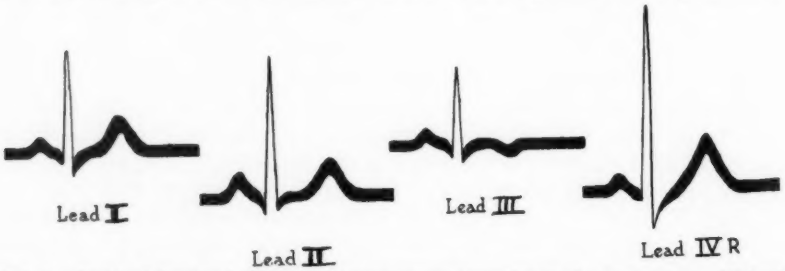

FIG. 5.—Standard four lead electrocardiogram drawn according to the mean values obtained in this series.

main part of the paper has been devoted to a detailed record and discussion of actual measurements of each component of the electrocardiogram.

In young women, each wave varies slightly from the values found by others for men and children ; both the voltage and duration appear to be intermediate, having in general lower values than in men and higher values than in children.

The classification of the components of the QRS deflection according to form has been a matter of some difficulty owing to the various views expressed by different authors. In describing Q and S it was found necessary to use the words inverted and fused, but we do not consider that the correct interpretation has yet been finally settled.

The form of R wave which we describe as diphasic is also a debated point. The other forms of R wave, however, were measured in accordance with the generally accepted view.

The S–T segment and S–T duration are studied separately in this paper. It was, however, difficult to ascertain the duration of the former on account of the frequency of the abrupt form which occurred mainly in lead IV.

The amplitude of T in lead I is a noticeable exception to our general conclusion that amplitudes have lower values in young women than in men. We regard as significant the frequent inversion of T in lead III.

Special attention has been paid to the findings in lead IV, and they have been compared with the other three leads.

Since we wrote this paper we have read the article by Chamberlain and Duncan Hay in this journal (1939). They made a study of 302 normal subjects, mainly in the third and fourth decades, and summarized the results in age groups covering seven decades. In general their values are similar to ours. We consider that the differences are accounted for by the fact that they investigated both sexes and a wider range of ages. In contrast with the 29 per cent. of inversion of T in lead III found by Chamberlain and Hay, we found 46 per cent. in our series of young women in their third decade.

We wish to express our grateful thanks to Professor Winifred Cullis, head of the Department of Physiology, and to Miss Marion Morris of the Department of Physics at the London School of Medicine for Women, for their help and advice.

To all students of the hospital who very kindly offered to collaborate, we are most indebted and greatly appreciate their help.

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ELECTRICAL AXIS DEVIATION OF FIFTY NORMAL ELECTROCARDIOGRAMS

BY

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In a single muscle fibre the electrical axis—the line along which the greatest electromotive force is developed at a given instant while the muscle is excited—is in the same line as the fibre itself. In a somatic muscle the electrical axis is also in the same line as the muscle itself (Lewis, 1925). In the heart muscle, however, the excitation wave spreads from a normal or abnormal pace-maker and the electrical activity takes a complex path and spreads simultaneously in different directions as the heart fibres run at many different angles.

The diffuse course can be represented by an axis—a curve not lying in a single plane, but in space, as does the heart itself. For clinical use, however, to suit the limits of electrocardiography, the axis is represented by its projection on the anterior plane of the body to fit the Einthoven triangle or the standard leads. Finally the curve is further simplified by constructing the projection of this line on each lead or side of the triangle, and the angle which it makes with one of the sides is briefly used to designate the electrical axis of the electrocardiogram.

The electrical axis can be calculated trigonometrically or by a simple clinical method. In this paper are given the results of measuring the axis deviation in the records from 50 normal female medical students (see Hoskin and Jonescu, pages 33–46 of this number).

Trigonometrical Method

The angle of deviation is calculated according to Einthoven's formula. The method is explained very clearly by Lewis (1925, p. 108). He points out that unless Einthoven's method is fully appreciated it is impossible to grasp the meaning and significance of these differences in the heights and directions of the deflections as they appear in the three body leads.

The size of angle varies according to the position of the arrow (heart electrical axis) in the triangle and its projection on the leads. Also the angle of the electrical axis varies slightly in relation to a given phase of the cardiac cycle. The direction of the resultant electrical axis of the heart lies within wider limits than does the anatomical axis in normal and abnormal hearts (Paul White, 1937).

The normal electrical axis lies between the degrees of 0 and 90. The axis deviations of our 50 normal electrocardiograms are shown in Fig. 1. If the

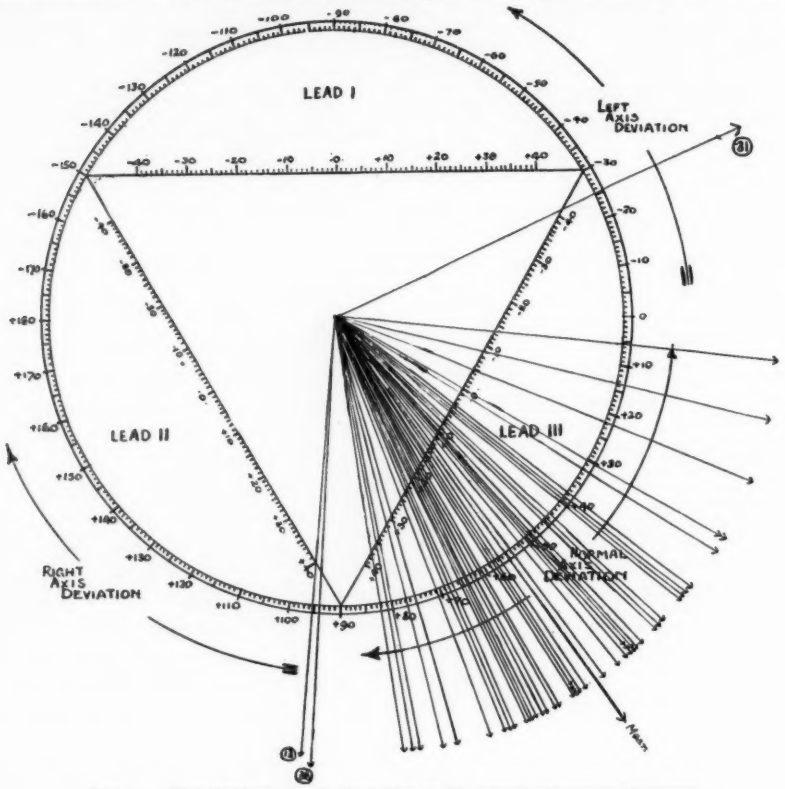

FIG. 1.—Distribution of axis deviation in 50 normal electrocardiograms.

angle has a minus value, that is above the horizontal line, or, in other words, if the arrow (electrical axis) in the Einthoven's triangle has shifted anti-clockwise, there is a so-called left axis deviation. If the angle has a value beyond 90° and the arrow (electrical axis) in the Einthoven's triangle has shifted clockwise, there is right axis deviation.

The frequency curve constructed from our analysis of the angles of axis deviation is reproduced in Fig. 2. The mean value for the angle of axis deviation was found to be +54·5°. It will be seen from Fig. 1 that in one record from a healthy athletic woman whose heart seemed normal (Case 31) there was an abnormal left axis deviation of −25°. Two records (Cases 13 and 38) showed a slight right axis deviation (+94° and +96°). The rest of the records show an angle within normal limits.

Paul White points out that it is more accurate to use the terms abnormal left and abnormal right axis deviation. Displacement upwards by a high

diaphragm so that the heart lies horizontally will give left axis deviation, even though the left ventricle remains normal. Similarly, a low diaphragm with a

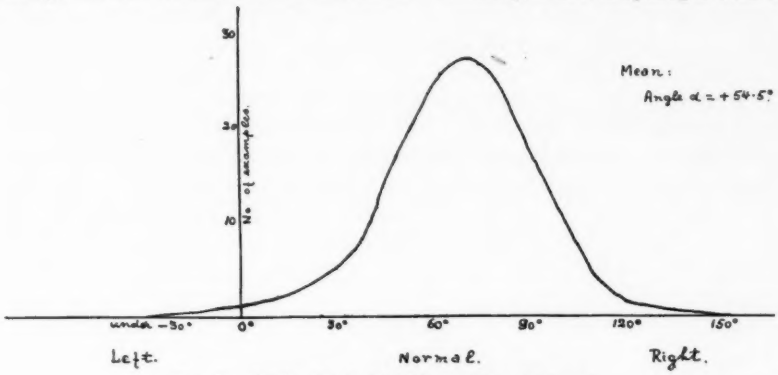

FIG. 2.—Angle of axis deviation : frequency curve.

vertical position of the heart will tend to give an abnormal right axis deviation, even though the right ventricle is small and the left ventricle may be preponderant. It is true, however, that a high degree of abnormal deviation is generally found with enlargement of the right or of the left ventricle ; though serious disease or enlargement of one or the other ventricle may be present with no evident abnormality of axis ; it is also true that when both ventricles are enlarged correspondingly, their effects tend to neutralize each other.

SIMPLE METHOD. INDEX OF AXIS DEVIATION

To estimate at a glance in clinical work the axis deviation, without the use of the trigonometrical method, the following formula is used :

$$\text{Index} = (R_1 + S_3) - (R_3 + S_1)$$

The index is derived by subtracting the sum of the amplitudes in millimetres of R in lead III and S in lead I from the sum of the amplitudes of R in lead I and S in lead III. According to Paul White, if the index measures over 30 mm., abnormal left axis deviation is present with a wide borderline of 20–30 mm. If the index measures under −15 mm., abnormal right axis deviation is present with a normal borderline of −10 to −15 mm. The analysis of index of axis deviation in our 50 normal subjects is reproduced in the following table :

INDEX OF AXIS DEVIATION IN 50 NORMAL CASES

	Range of Index in mm.	Percentage of Total
Right	−15 to −10	4
	−10 to −5	10
	−5 to 0	28
	0 to 5	24
	5 to 10	20
	10 to 15	6
	15 to 20	6
	20 to 25	0
Left	25 to 30	2

The mean value was +2·45 mm. One record (Case 31) showed left axis deviation that was almost abnormal (25–30 mm.) and three records (Cases 20, 21, and 45) showed slight or borderline left axis deviation (15–20 mm.). Two records (Cases 43 and 49) showed slight or borderline right axis deviation. The examination of the table and curves shows that in general both methods—the trigonometrical and the simple—agree, but that the trigonometrical is much more accurate. It will be seen that one electrocardiogram (Case 13) is shown by the trigonometrical method to be of right axis deviation, but by the simple method is found to be within normal range (index = −8). Also that the 5 records (2 of which were borderline right axis and 3 borderline left axis) are found to belong to the normal range of electrical axis deviation by the trigonometrical method.

Summary

The results of the measurements of the axis deviation of the electrocardiograms taken from 50 normal women students at the Royal Free Hospital have been measured and reported.

A comparison of the trigonometrical method and of a simple clinical method of calculation shows that there is a general agreement. The former is, of course, more accurate but the latter can be calculated quickly and easily and is accurate enough to be of practical use.

We wish to express our thanks to Professor Winifred Cullis and Miss Marion Morris from the London School of Medicine for Women for their valuable help and advice and to the students of the Royal Free Hospital for their kind collaboration.

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THE RELATIVE VALUE OF CERTAIN DIGITALIS PREPARATIONS IN HEART FAILURE WITH AURICULAR FIBRILLATION

BY

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Digitalis is given universally in heart failure with auricular fibrillation, and to prevent the recurrence of failure it is the custom to continue it. Yet there is still doubt as to the best preparations to use and the dosage to maintain adequate digitalization. In this paper a clinical assay is attempted, based on a study of subjective and objective symptoms, and the results have been controlled by comparison with less potent remedies, both within and without the digitalis group. The place of digitalis in failure with normal rhythm has long been discussed, among others by Mackenzie (1911), Lian (1926), and Luten (1936), and more recently in this department by Gavey and Parkinson (1939). Here, however, I am dealing only with patients suffering from auricular fibrillation of rheumatic origin as proved by the coincidence of mitral stenosis.

Eighteen of the 25 patients accepted as suitable remain for the complete analysis : the other 7 failed to finish the entire schedule of the investigation ; one died at another hospital, two were admitted with pulmonary infarction, two left the district and were unable to attend, while two were omitted because the heart rhythm became normal even though they were under treatment with digitalis. The 18 patients consisted of 6 men and 12 women ; their ages varied from 25 to 59, with an average of 48 years. After routine clinical examination which included electrocardiography and radiocardioscopy they were chosen as comparable cases, in that they had in common three lesions—mitral stenosis, auricular fibrillation, and heart failure.

They were treated solely as out-patients and many of them followed their usual occupation. As a rule they attended hospital fortnightly, but occasionally they returned earlier on account of fresh symptoms. A different preparation was prescribed for each test period of 14 days, but never in the same rotation. At each attendance a record was made of the patient's activities and progress during the past test period, when any symptoms of heart failure or any toxic effects were noted, and a detailed clinical and graphic examination was carried out at intervals. After a brief rest at each interview, the pulse and heart rates were counted over half-minute periods and the mean of three

consecutive readings was accepted. Although in this way there was a record for each patient of the *change in heart rate* following each medicine, it was clear that the drug could not be assessed on this criterion alone. For instance, the tincture of digitalis during a period following coramine might reduce the heart rate by 50 beats a minute, while if it followed a test period on digitalis leaf the heart rate might actually rise by 10 beats. This difficulty was partially avoided by prescribing the drugs in different sequence. It was found, however, that much greater reliance could be placed on a comparison of the *actual heart rate* at the end of each test period, for then the influence of the preceding drug was no longer operative. Further, the extent of heart failure, determined by symptoms and by clinical and radiological examination, tallied so closely with the heart rate that this came to be accepted as a reliable index of the state of digitalization for each patient. The heart rate following different preparations may be compared in the same patient, but the rate from the same preparation is not comparable in different patients. Depression of the R–T segment in the electrocardiogram proved that digitalis was in action and to some extent indicated its hold on the heart.

The following preparations were tested : digitalis leaf, tincture of digitalis, digoxin, digitaline (Nativelle), digitaline (Allen & Hanbury), digifoline, folinerin, strophanthin, and ouabaïne ; cardiazol and coramine were used as controls. The digitalis preparations were dispensed, in comparable doses in terms of biological assay, in some cases twice and in others three or even four times a day according to the judgment of each patient's need ; but the number of daily doses of any preparation was kept constant for each individual patient. The medicines were given for 14 days : with the one exception that cardiazol and coramine were given for 7 days only, because it was found unsafe to leave patients taking either of these drugs without medical supervision for as long as 14 days ; in reality it was digitalis they needed. Before giving an account of the results, the procedure adopted will now be instanced in one patient.

J. W., male, aged 45. Palpitation and breathlessness for several months, yet at work as a tailor until two weeks before admission when severe palpitation caused him to give it up. On examination : Rather stout. Slight cyanosis and breathlessness, increased in recumbent position. Blood pressure normal. Distension of veins of neck. Electrocardiogram, auricular fibrillation. Heart rate 164, pulse rate 124 a minute. Apex beat forcible and slightly displaced outwards. Harsh diastolic murmur in mitral area. Coarse and fine crepitations over both lung bases especially right. Liver not enlarged and no œdema of ankles. Urine trace of albumen ; daily output satisfactory. Radiogram, characteristic of mitral stenosis and heart failure. Satisfactory response to rest and digitalization during five weeks in hospital. Then referred to out-patient department and received into this series. Each medicine was given to the patient three times daily and his further progress is tabulated on the next page.

Date	Medicine during current test period	Dose given 3 times a day	Rate at end of test period		Patient's statement on progress
			Pulse	Heart	
5 January	Digitalis leaf	1½ grains	64	66	Well
19 ,,	Digitaline (Allen & Hanbury)	1/240 grain	68	76	Fair
2 February	Digitalis tincture	15 minims	66	76	Fair
16 ,,	Digoxin	0·25 mg.	76	80	Well
2 March	Strophanthin	1/100 grain	72	88	Well
16 ,,	Folinerin	0·1 mg.	80	92	Not well
30 ,,	Digifoline	1 tablet	70	74	Fair
13 April	Ouabaïne	1 mg.	70	94	Fair
20 ,,	Coramine	1 drachm	80	110	Not well
27 ,,	Cardiazol	1½ grains	88	104	Not well
4 May	,,	,,	100	108	Not well
28 ,,	Digitalis leaf	,,	72	72	Better
25 June	,, ,,	,,	68	92	Fair
23 July	,, ,,	,,	64	68	Fair
6 August	Digitaline (Nativelle)	1/240 grain	56	56	Nausea + + Discontinued after 5 days
20 ,,	,,	1/600 grain	60	60	Better
3 September	Ouabaïne	5 mg.	77	76	Better
1 October	Digitalis leaf	1½ grains	80	80	Well

Results of Observations

The results for each preparation are first given, and then the several preparations are compared. They are summarized in Tables I and II.

TABLE I

Heart Rate (per minute) in 18 Patients with Auricular Fibrillation after Treatment

Patient					Preparation Used										
Case Number	Age	Sex	Weight (in lb.)	No. of Doses Daily	Digitalis leaf	Digitaline (Nativelle)	Digifoline	Digoxin	Tincture of Digitalis	Digitaline (A. and H.)	Folinerin	Ouabaïne	Strophanthin	Coramine	Cardiazol
1	55	F	106	2	87	88	88	86	96	86	92	82	94	100	108
2	25	F	104	3	65	72	72	70	80	66	96	80	104	86	110
3	56	F	134	3	60	72	72	80	108	80	96	116	92	94	116
4	41	F	98	4	74	84	75	92	78	85	80	134	150	124	128
5	49	F	149	3	98	80	88	98	92	86	110	120	108	134	106
6	45	M	200	3	68	60	74	80	76	76	92	76	88	110	104
7	44	M	184	3	80	84	78	80	110	88	76	84	110	96	98
8	65	F	114	2	64	78	100	98	84	98	90	100	92	152	140
9	48	M	116	2	52	50	56	56	58	64	46	66	74	78	78
10	53	M	147	3	104	115	116	120	88	118	140	108	130	128	135
11	51	M	135	3	70	46	62	66	90	68	104	80	84	114	96
12	58	F	182	2	74	74	92	76	62	84	106	116	106	98	112
13	46	F	84	2	52	62	72	64	72	84	100	124	130	100	130
14	53	F	98	2	80	80	98	88	76	100	72	110	146	90	122
15	37	F	104	3	74	80	78	94	106	94	88	94	90	96	126
16	54	F	154	2	66	102	100	92	70	86	92	88	98	112	120
17	42	F	185	2	84	88	70	77	96	96	98	92	104	104	150
18	59	M	147	2	94	102	120	106	126	110	136	128	120	154	136

Powdered digitalis leaf

Mackenzie (1911) chose to use either the tincture or the powdered leaf, and preference for the latter has been expressed by Wenckebach (1930), White (1931), Luten (1936), Fishberg (1937), and Gavey and Parkinson (1939).

Taking the cat unit as the minimal dose, per kilogram of cat-weight, proving lethal from slow intravenous injection of digitalis, it is estimated that 1 1/2 grains of well dried and undeteriorated powdered leaf contain a single cat unit. This dose was always given as a tablet composed of pulvis digitalis folia (B.P) which is comparable with that in the United States Pharmacopœia (1936). Campbell (1938) thinks that in clinical practice digitalis leaves are stronger than when estimated from animal experiments and on the basis of clinical observations advises that tab. dig. fol. gr. i., rather than gr. 11/2, can be taken as a close equivalent of 15 minims of the tincture.

The heart rate at the end of the test periods varied from 54 to 104 a minute with an average of 75 for the 18 patients. This proved to be the lowest level obtained from any preparation tried. Similarly the powdered leaf proved its superiority when its value was based on the reduction of the rate from the preceding period. A reduction was effected in 17 patients with an average fall of 19 beats a minute, the maximum fall being 46.

Clinical improvement was invariably produced, and nausea was only reported once.

Tincture of digitalis

Bramwell (1932) prefers standardized tincture of digitalis to any other preparation. Lewis (1934) states that as a routine the tincture should be used.

Since 15 minims of the 10 per cent. tincture represent one cat unit of digitalis, it equals 1 1/2 grains of the powdered leaf and therefore it was prescribed in this dose.

The heart rate at the end of the test periods varied from 58 to 126 with an average of 87 beats a minute. When the change in the rate from the preceding period was studied, it was found lowered in 8, increased in 8, and unchanged in 2 patients. The greatest fall was 64 and the greatest rise 32 beats a minute while the average for all patients was a fall of 3.

Clinical improvement was noted in every case. Nausea occurred in 3 patients.

Digitaline (Nativelle)

This is a glycoside derived from the leaves of the foxglove, *Digitalis purpurea*, and is said to be a chemical entity, constant in its physical characters and chemical reactions, and not requiring physiological standardization. It is usually dispensed as white and pink granules, the white granule containing 1/240 grain (0·25 mg.) and the pink granule 1/600 grain (0·1 mg.). Mackenzie (1911) compared the clinical effects of the tincture of digitalis with Nativelle digitaline, and found that 1/240 grain (white granule) of digitaline was equal to

15 minims of the tincture. Campbell (1938), from clinical observations, concluded that 1/600 grain (pink granule) of Nativelle digitaline was equivalent to 15 minims of the tincture of digitalis. Stroud and Vander Veer (1937) reported on five preparations of digitalis observed over a period of six years. On comparing verodigen, a gitalin glycoside of digitalis, with digitaline (Nativelle) they found that 1/600 grain of the latter produced the same clinical effects as 1/240 grain of the former.

In the present series digitaline (Nativelle) was first tried in a dose of 1/240 grain (white granule). Without exception it produced severe nausea and vomiting between the second and fifth day and had to be discontinued. Most of these patients reported prematurely to hospital, when the heart rate was found to be very slow ; though a few returned at the end of the prescribed test period, when the rate was more rapid from the lack of digitalis therapy for eight or more days. Later it was decided always to use the pink granule containing 1/600 grain.

The heart rate at the end of the test periods varied from 46 to 115 a minute with an average of 79. When its value was based on the reduction of the rate from the preceding period, it was found lowered in 15 patients, raised in 2, and unchanged in another. The greatest fall was 50 and the greatest rise 10 beats a minute, while the average for all the patients was a fall of 12.

Clinical improvement was noted in every patient, and toxic symptoms were never reported from the pink granule (1/600 grain).

Digitaline (Allen & Hanbury)

This preparation, said to consist of the active principle of the foxglove, is supplied as pink and white granules similar in appearance and dosage to those of Nativelle digitaline. For this investigation only the white granule of 1/240 grain was used.

After its administration for test periods of 14 days the heart rate varied from 64 to 118 a minute, with an average of 87. When its value was judged by the reduction of the heart rate from the preceding period, it was lowered in 7 patients, raised in 8, and unchanged in 3. The greatest fall was 22 and the greatest rise 24 beats a minute, while the average was a rise of 3.

Efficient digitalization was obtained in every patient, and toxic effects were never seen.

Digifoline

This standardized preparation made by Ciba is said to contain all the therapeutically active glycosides of digitalis leaf. Each tablet is claimed to be equivalent to 1 1/2 grains (0·1 g.) of the standard digitalis leaf so this dose was used.

At the end of the test periods the heart rate varied from 56 to 115 with an average of 84 beats a minute for all the patients. When it was evaluated by the reduction of the rate from the preceding period, it was lowered in 15 patients

raised in 2, and unchanged in another. The greatest fall was 42, the greatest rise 10, and the average was a fall of 15 beats a minute.

Digifoline never occasioned toxic symptoms and efficient digitalization was established in every patient.

Digoxin

Digoxin, a crystallized glycoside isolated from the leaf of *Digitalis lanata*, is prepared by Burroughs Wellcome and is said not to require biological standardization. Each tablet contains 0·25 mg.

The heart rate at the end of the test periods varied from 56 to 120, with an average of 85 beats a minute for all patients. When its efficiency was calculated from the reduction of the rate from the preceding period, it was found to be lowered in 10 patients, raised in 7, and unchanged in another. The greatest fall was 36 and the greatest rise 14, while the average for all patients was a fall of 8 beats a minute.

Clinical improvement was always obtained, but anorexia was noted once.

Folinerin

Folinerin, prepared by Schering, is a crystalline glycoside obtained from the eaf of *Nerium oleander*, and a digitalis-like action is claimed for it. Each tablet contains 0·1 mg.

The heart rate at the end of the test periods varied from 46 to 140, with an average of 95 beats a minute. When its value was judged by the reduction of the rate from the preceding period, it was found to have been raised in 10, lowered in 6, and was unchanged in 2 patients. The greatest rise was 38 and the greatest fall 32, while the average change was a rise of 3 beats a minute.

No toxic symptoms were observed, but noticeable clinical improvement was only recorded in 2 patients.

Strophanthin

Strophanthin, a glycoside isolated from the seed of *Strophanthus kombé*, is seldom used in this country for the continuous treatment of heart failure. Tablets, each containing 1/100 grain, were used.

The heart rate at the end of the test periods varied from 74 to 150 beats a minute, with an average of 106 for all the patients. When the efficacy of the drug was judged by the change of rate from the preceding period, a rise had taken place in 15 patients, a fall in 2, and there was no change in 1 patient. The greatest rise was 36 beats a minute and the greatest fall 6, while the average for all patients was a rise of 13.

In 5 patients the symptoms of heart failure increased during the test period on strophanthin, and none showed any clinical improvement.

Ouabaïne

Ouabaïne, a strophanthin glycoside isolated from the *Strophanthus gratus*, has a different formula from ordinary strophanthin. Tablets containing 5 mg. (1/12 grain) were used.

The heart rate at the end of the test periods varied from 66 to 134 beats a minute, with an average of 100 for the 18 patients. When its value was judged by the change of rate from the preceding test period, a rise was found to have taken place in every patient ; the greatest rise was 64 beats a minute and the average 22.

Five patients complained of headache, depression, and breathlessness. Clinical improvement was not once recorded.

The results obtained with the different preparations are summarized in Table II.

TABLE II

THE CHANGE IN HEART RATE IN 18 PATIENTS WITH AURICULAR FIBRILLATION FOLLOWING TREATMENT

Medicine prescribed	Average Heart Rate for 18 patients at end of test periods	Number of Patients where the Heart Rate was			Net average of Change of Heart Rate
		Lowered	Unchanged	Raised	
Digitalis leaf	75	17 (20)*	0	1 (2)*	−19
Digitaline (Nativelle)	79	15 (15)	1	2 (8)	−12
Digifoline	84	15 (19)	1	2 (6)	−15
Digoxin	85	10 (19)	1	7 (6)	−8
Tincture of digitalis	87	8 (24)	2	8 (16)	−3
Digitaline (Allen&Hanbury)	87	7 (6)	3	8 (14)	+3
Folinerin	95	6 (14)	2	10 (14)	+3
Ouabaïne	100	0 —	1	17 (23)	+22
Strophanthin	106	2 (4)	1	15 (16)	+13
Coramine	109	0 —	2	16 (26)	+21
Cardiazol	117	1 (8)	2	15 (23)	+19

* The figures in brackets show the average reduction or rise, in beats per minute.

Cardiazol

Cardiazol or metrazol has a formula related to camphor, and by some it has been acclaimed as a " heart stimulant " that reduces the heart rate and increases the venous flow, coronary flow, and the cardiac output. Cardiazol was tested, not in the belief that it possesses a digitalis-like action, but rather as a comparison with the other drugs. It was given orally as tablets containing 1 1/2 grains (0·1 g.), but the test period of 14 days was reduced to 7 for it became evident after trial that it was unsafe to withhold digitalis from patients in this series for longer than a week.

The heart rate at the end of the test periods varied from 78 to 150 beats a minute, with an average of 117 for the series. When its value was estimated from the change of rate from the preceding period, there was a rise in 16 patients. The greatest rise was 48 beats a minute and the average 19.

Breathlessness, palpitation, weakness, and headache, appeared in 9 patients, and clinical improvement was not once recorded.

Coramine

Coramine, reputed to be a "cardiac stimulant," is widely used. It was given orally to each patient in this series in the optimum dose of 30 minims (2 c.c.); but, like cardiazol, it was included more as a control than for its alleged value. As with cardiazol, it was found unsafe to allow patients taking it to be without medical supervision for more than 7 days, by which time the lack of digitalis had become evident.

The heart rate at the end of the shorter test periods varied from 78 to 154 beats a minute, with an average of 109 for all patients. When its value was judged by the change of the rate from the preceding period, a rise was recorded in every case. The greatest rise was 62 beats a minute and the average 21.

Headache was distressing in 7 patients and clinical improvement was not once recorded. In 15 patients the symptoms of heart failure reappeared during its administration.

The shorter test period adopted for cardiazol and coramine has to be taken into account when comparing their influence on the heart rate and their clinical effects with those of digitalis preparations, because the recorded rates would be much higher after the standard and longer test period and the symptoms of heart failure correspondingly greater.

Discussion of Results

The scarcity of controlled observations on the clinical effects of various digitalis preparations prompted this inquiry into their relative value. Mackenzie (1911) compared the effects of the tincture with Nativelle digitaline and a pill containing powdered digitalis leaf, squills, and mercury. He watched for the first sign of a digitalis reaction and then noted the quantity of the drug which had induced it. In 1925 Cushny deprecated the fact that even though many preparations were employed, little had been done in the way of accurate comparison of their effects in man. Luten (1936) stated that on the basis of both animal experiments and clinical experience there was no valid reason for preferring one particular digitalis preparation to another on the grounds of some alleged selectivity of action on the heart.

The right choice of a preparation and of dosage will not be decided from experiment in animals, but from such comparison in patients as is attempted in the present investigation. When judged by amelioration of failure symptoms, freedom from toxic effects, and decrease in the heart rate, 6 of the 11 preparations tried proved satisfactory. Arranged in the order of therapeutic efficiency when used in customary doses, they were: powdered digitalis leaf, digitaline (Nativelle), digifoline, digoxin, tincture of digitalis, and digitaline (Allen & Hanbury). Three preparations, folinerin, ouabaïne, and strophanthin, never produced satisfactory digitalization, and their routine use in patients with heart failure is unjustified. As to cardiazol and coramine, which served to control the observations on the other drugs tried, it was not expected that either would reduce the heart rate or master the symptoms of failure, but it was

surprising to find that, apart from not benefiting a single patient, they induced ill effects so frequently. It is clear that neither cardiazol nor coramine have any place in the *continuous* treatment of heart failure. The comparison is well shown in Fig. 1, which also indicates the cost of treatment and shows that the more effective preparations are not the more expensive ones.

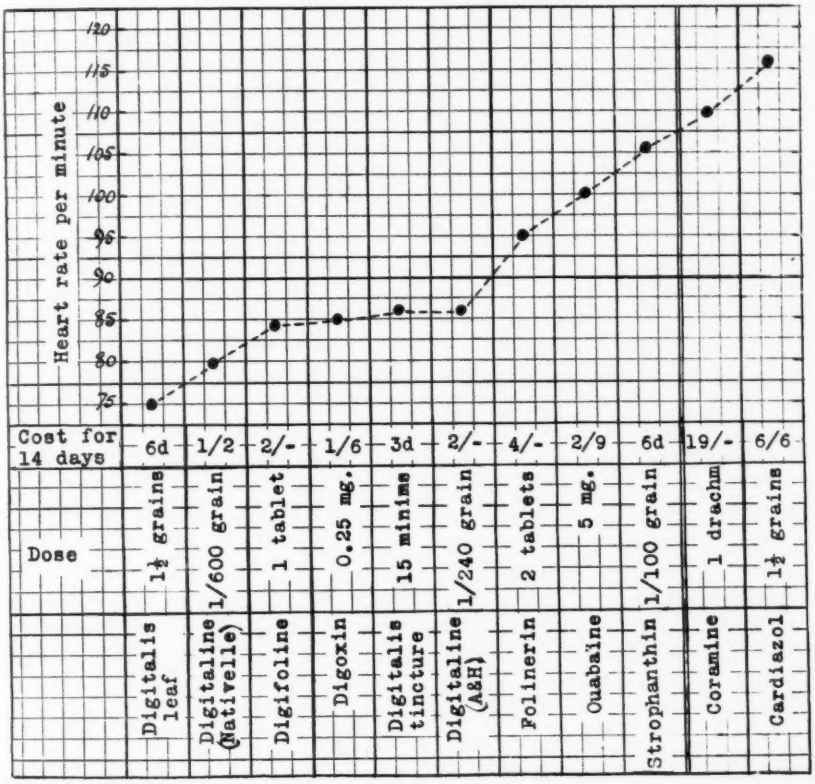

FIG. 1.—The effect of drugs on the heart rate in 18 patients with auricular fibrillation. An average rate of 90 has been accepted as the uppermost level of satisfactory digitalization for this series. The cost of each drug is quoted, for hospital patients receiving it three times a day for a fortnight. Drugs to the left of the upright double line were given over periods of 14 days; those to the right, over periods of 7 days.

The dosage of digitalis for ensuring adequate digitalization has long been in dispute, but most authorities think that it must be determined separately in each patient. Withering's (1785) opinion was that digitalis should be continued until it acted on the kidneys, stomach, pulse, or bowels, when it should be stopped. Mackenzie (1911) said that patients instructed on the symptoms indicating a sufficiency of the drug could generally help thereby to decide the dosage that suited them. Eggleston (1915 and 1920) devised a formula for

estimating the amount of digitalis required to produce a state of digitalization, founded on the body weight and the amount of digitalis preparation to one cat unit.

In a clinical investigation of digitalis action, Lyon and Gilchrist (1927) found wide variation in the effects of uniform doses as calculated from the body weight. Baker and Bloom (1936) found that the experimental cat unit was not a reliable index of the proper clinical dosage, nor could this be determined in patients by means of Eggleston's formula. Luten (1936) said that the optimum dose of digitalis, whether for the induction of its effects or for its maintenance, should be judged individually ; and he urged that no patient should receive an arbitrary dose in an attempt to bring about some anticipated effect, but rather that the effect produced must always determine the dosage.

This investigation has confirmed the view that the dosage of digitalis cannot be predicted for each patient and that it can only be settled after clinical trial. Evidence is produced that it is not possible to calculate the appropriate clinical dose of any digitalis preparation from biological standardization, nor yet from the patient's body weight. Thus digitalization of a patient of heavy weight was sometimes maintained by small doses of digitalis, while that of a patient of light weight was often only reached by larger doses (see Table I).

Throughout the investigation the *single* dose of each preparation was kept constant, as was the *daily* dose for an individual patient, but all did not receive an identical amount, and the decision on this had to be taken in each case after a preliminary clinical trial. Thus for powdered digitalis leaf a dose of 1 1/2 grains was always prescribed, but the daily dose was twice a day in 9 patients, three times a day in 8, and four times a day in 1 patient.

The fallacy of deducing the value of a digitalis preparation from a comparison of its effect upon heart rate in different patients became more apparent as the investigation proceeded. True evaluation must therefore depend on a *comparison* of the heart rate after treatment with *different* preparations in the *same* patient. In fact, the heart rate during successful digitalization differs widely among patients with auricular fibrillation (see Table I). In one a satisfactory rate was 115, but in another 52 beat a minute, directing our greater attention to the abatement of failure symptoms and the reduction of the pulse deficit as the indications of improvement.

In this country four manufacturing chemists supply *digitaline* granules that are similar in colour and dosage to those prepared by Nativelle. Although the dosage is the same, the therapeutic effect may differ greatly ; and certainly of the two brands tested in this investigation, Nativelle digitaline produced digitalis benefit that was twice as great as that gained from Allen and Hanbury's digitaline. One must, therefore, know which product is being used, so that an appropriate amount may be ordered.

Conclusions

The effects of six preparations of digitalis and of three others with a digitalis-like action were watched in eighteen comparable cases of auricular

fibrillation with mitral stenosis and heart failure. Each preparation was tried in every patient, and its value was assessed at the end of test periods of fourteen days, with due regard to the heart rate, pulse deficit, failure symptoms, toxic effects, and electrocardiographic changes. The observations were controlled by introducing test periods during which digitalis was not given in any form and cardiazol or coramine were the only drugs prescribed. The following conclusions were reached :

1. Efficient digitalization was always induced and maintained by powdered digitalis leaf, digitaline (Nativelle), digifoline, digoxin, tincture of digitalis, and digitaline (Allen & Hanbury), mentioned in the order of their therapeutic activity in customary doses and from a practical standpoint.

2. Powdered digitalis leaf proved to be the best preparation for maintaining equable digitalization. It was also one of the cheaper preparations.

3. Digitaline (Nativelle) in a dose of 1/600 grain (pink granule) showed greater digitalis effect than digitaline (Allen & Hanbury) in a dose of 1/240 grain (white granule). Digitaline (Nativelle) in a dose of 1/240 grain (white granule) proved too potent for continuous use.

4. Folinerin, ouabaïne, and strophanthin (orally) failed to produce adequate digitalization and their routine use in heart failure is not justified.

5. Symptoms of heart failure developed in every patient when either cardiazol or coramine was prescribed without digitalis.

6. The actual heart rate was found to be an unreliable index of successful digitalization ; thus for one patient it was 115 during a period of maintained clinical improvement and for another 52 beats a minute. The heart rate gains the greatest significance when the digitalis effect of different preparations is estimated in the same patient. Freedom from symptoms and signs of heart failure served best to indicate successful digitalization.

7. It proved a good custom to adopt a standard dose for each digitalis preparation and to vary only the total daily dosage. Thus with powdered digitalis leaf, the single dose of 1 1/2 grains was always employed, but this was given either twice, three times, or four times a day, according to need.

8. The optimal dose of digitalis could not be predicted with any accuracy, and it had to be sought by trial and error, thus implying a therapeutic study in every patient.

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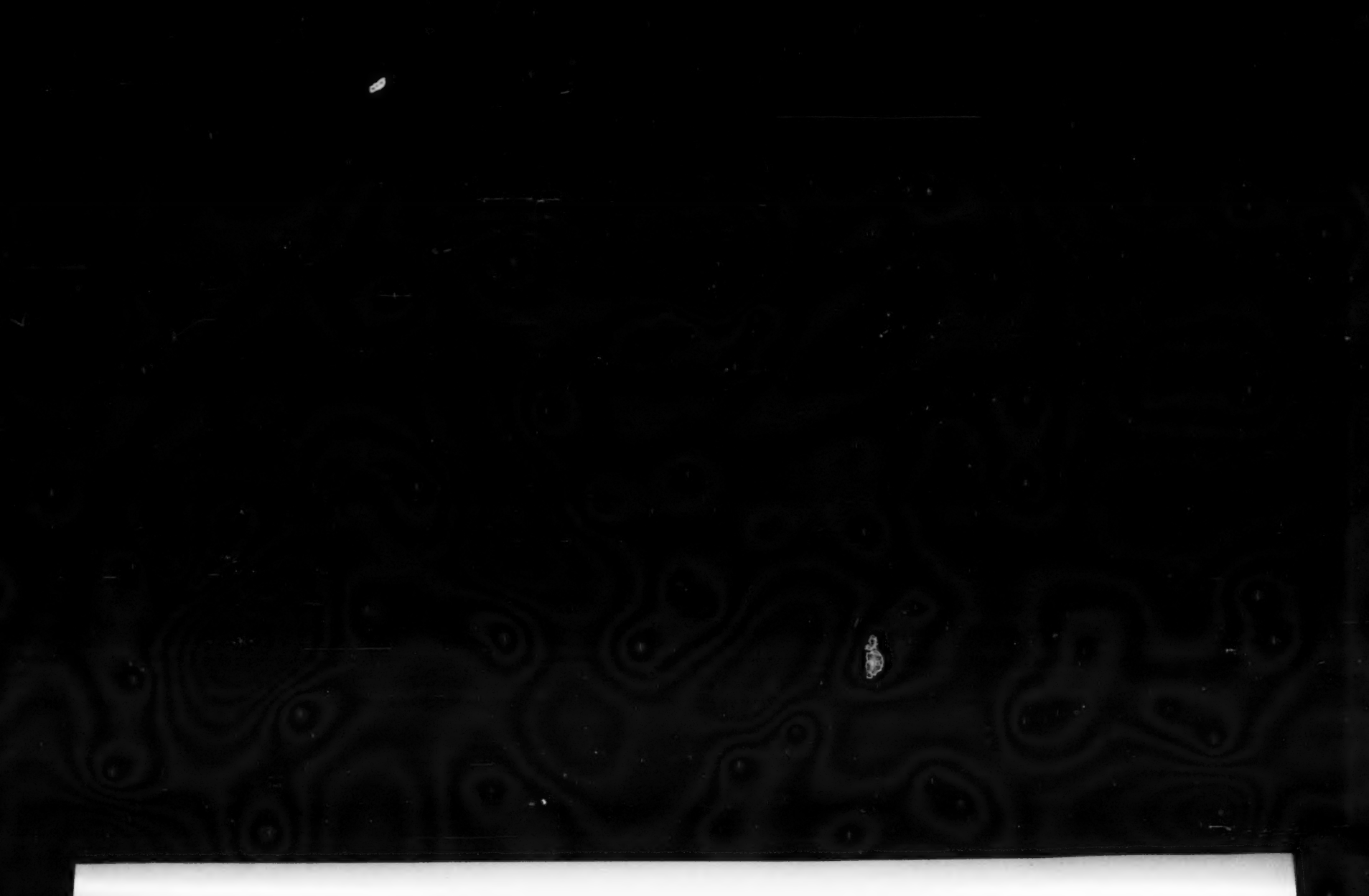
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